Family planning considerations in people with multiple sclerosis

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See **Comment** page 288

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Multiple sclerosis is often diagnosed in patients who are planning on having children. Although multiple sclerosis does not negatively influence most pregnancy outcomes, less is known regarding the effects of fetal exposure to novel disease-modifying therapies (DMTs). The withdrawal of some DMTs during pregnancy can modify the natural history of multiple sclerosis, resulting in a substantial risk of pregnancy-related relapse and disability. Drug labels are typically restrictive and favour fetal safety over maternal safety. Emerging data reporting outcomes in neonates exposed to DMTs in utero and through breastfeeding will allow for more careful and individualised treatment decisions. This emerging research is particularly important to guide decision making in women with high disease activity or who are treated with DMTs associated with risk of discontinuation rebound. As increasing data are generated in this field, periodic updates will be required to provide the most up to date guidance on how best to achieve multiple sclerosis stability during pregnancy and post partum, balanced with fetal and newborn safety.

Introduction

Multiple sclerosis predominantly affects women; over the past four decades, the female to male incidence ratio has increased to around 2:1–3:1.[1] The disease is most commonly diagnosed between the ages of 20 years and 45 years, when considerations around family planning are of importance to many people. Most women with multiple sclerosis can have safe pregnancies and healthy children. However, the increasing number of available disease-modifying therapies (DMTs)—some with teratogenic potential—alongside a move towards early effective treatment, has introduced complexity into family planning.

A relative remission in multiple sclerosis disease activity during pregnancy is often relied on by neurologists and patients.[2] However, the immunological changes of pregnancy are not sufficient to protect women who withdraw from DMTs such as natalizumab or fingolimod, from severe disease reactivation.[3,4] Importantly, the risk of post-partum relapse has decreased over recent years, with between 14% and 31% of women relapsing in the 3 months post partum in modern (2010 and later) and historical (before 2004) cohorts, respectively.[2,5,6]

The management of active multiple sclerosis in women planning a pregnancy or discovering an unplanned pregnancy remains one of the most challenging aspects of clinical management. Regulatory approvals around pregnancy and breastfeeding are often conservative and restrictive. Establishing the reproductive toxicity of drugs via inadvertent exposure can take decades. For instance, European regulatory advice for interferon beta was only changed in 2019, almost 25 years after its original approval by the European Medicines Agency. Many physicians and women opt to interrupt medication, often before starting to try to conceive, due to a focus on possible drug-related harms. This behaviour can lead to therapeutic inertia in women with multiple sclerosis of childbearing age, resulting in women not being treated or offered fewer or less effective treatment options because they want to have children.[7] The situation is also problematic for breastfeeding, whereby default counselling is often to forego breastfeeding despite well-known health benefits for both the mother and child. Fortunately, label changes or approvals in the last 5 years specifically consider breastfeeding safe in women treated with some DMTs.

Proactive discussion with women and their families is essential and requires careful consideration. The aim is to obtain an optimal balance between the risks of suspending multiple sclerosis treatments and avoiding the adverse effects of DMTs on the fetus. This balance is not equal for all women, given the heterogeneity in disease activity and differing DMT profiles around pregnancy. Risk estimates in modern cohorts (2010 and later) of pregnant women with multiple sclerosis with different DMT exposures have been published in the past 5 years,[3,5] along with an increasing amount of safety data on drug exposure during both pregnancy and breastfeeding.

This Review on family planning in multiple sclerosis provides an updated and comprehensive overview of aspects of relevance to women and men with multiple sclerosis who are planning to have a family. We discuss fertility and contraception, and counselling before, during, and after pregnancy. Additionally, we evaluate findings on the short-term and long-term risk of relapse during and after pregnancy. Furthermore, we provide updated safety information and recommendations on DMTs during pregnancy and breastfeeding. Importantly, gender is a socially constructed category, and people with multiple sclerosis whose identity is different from woman or mother can become pregnant and breastfeed. Our Review reflects the available data on female patients who identify as women and mothers, while recognising the need for more inclusive research and terminology.

Family planning: non–DMT aspects

Fertility

Fertility does not seem to be directly affected by multiple sclerosis.[8] Lower pregnancy and birth rates in women

with multiple sclerosis than in age-matched individuals without multiple sclerosis have been observed in the years before and subsequent to diagnosis,[9–11] possibly reflecting the physical and psychological impact of early multiple sclerosis.[10] Other studies have shown a minor increase in birth rate in people with multiple sclerosis over time; one hypothesis is that increasing access to DMTs is changing reproductive behaviours. In men, a large linkage study showed a potential association between male infertility and an increased risk of multiple sclerosis,[12] but more conclusive studies are needed. Older chemotherapy-based treatments that are now rarely used (eg, mitoxantrone and cyclophosphamide) can affect fertility in both women and men.

Women with subfertility or infertility might undergo assisted reproductive technology (ART).[8] Historical case series summarised in a meta-analysis suggested an elevated relapse rate in women with multiple sclerosis following ART, particularly with gonadotrophin releasing hormone agonist protocols or unsuccessful cycles.[13] Larger, more recent studies published in the past 5 years, including a cohort of 12 women with 22 ART cycles[13] and a population-based study of 225 women with 338 in vitro fertilisation (IVF) cycles,[14] did not show this elevated relapse rate, which was likely related to evolving DMT use and ART techniques, alongside changing diagnostic criteria. Women with multiple sclerosis should not be advised against ART and should be offered the approach with the highest chance of success, alongside aiming for optimum disease control with a pregnancy-compatible DMT.

Sexual and bladder dysfunction, pain and depression, and patient concerns about disability and disease course also affect family planning.[9,15] Addressing these factors is crucial as part of holistic treatment.

Contraception

Studies report conflicting results regarding use of oral contraception on the risk of multiple sclerosis; however, no association between oral contraceptive use and subsequent increased risk of multiple sclerosis has been consistently reported.[16] Oral contraception use before or after clinically isolated syndrome does not significantly influence the risk of conversion to multiple sclerosis or of disability development.[17]

Contraception should be regularly discussed with people with multiple sclerosis. The most effective reversible contraceptive methods are long-acting, reversible contraceptives, including intrauterine devices and implants. Most methods can be used without restriction in patients with multiple sclerosis; however, combined hormonal contraceptives might increase the risk of venous thromboembolism, which is particularly relevant in those who have mobility limitations or who are treated with corticosteroids. These highly effective methods are preferable for people receiving potentially teratogenic medications.

Available studies show no significant pharmacokinetic interaction between oral contraception and oral DMTs.[18,19] Potential reduced absorption of oral contraception as a result of dimethyl fumarate-related diarrhoea or accelerated elimination protocols for teriflunomide must be considered. Modafinil could decrease the effectiveness of hormonal contraceptives, and some antiepileptic drugs used for pain or paroxysmal symptoms might interact with hormonal contraceptives.

Supplements

Timely initiation of folic acid (≥3 months before trying to conceive) and adequate vitamin D supplementation before conception and during pregnancy (maximum 4000 IU per day) should be advised. Iron supplementation might be required when women develop anaemia before or during pregnancy; if oral iron is used, care should be taken to avoid constipation.

Vaccinations

Pregnant individuals are at increased risk of infections and are a priority group for vaccination. Live-attenuated vaccines are contraindicated during pregnancy, whereas inactivated vaccines are generally considered to be safe. Adequate vaccine titres, including those important during pregnancy (eg, rubella), should be confirmed before starting anti-CD20 therapies or S1P receptor modulators. Although anti-CD20 therapies and S1P receptor modulators might reduce vaccine response, women should still be encouraged to access non-live vaccinations. Data on vaccine response in offspring are not yet available. Influenza and pertussis vaccinations during pregnancy are specifically recommended in all women by the National Health Service in the UK. COVID-19 vaccination can be safely given during pregnancy and breastfeeding.[20,21]

Birth choices and neonatal outcomes

Having multiple sclerosis should not influence obstetric management outside of considerations related to disability and, possibly, fatigue. Women with multiple sclerosis are often advised that their pregnancies should be treated as high risk but, outside of disability considerations, this is not necessarily the case. Exposure to potentially teratogenic medication or use of monoclonal antibodies during the second and third trimester of pregnancy might require closer monitoring than usual. Although women with multiple sclerosis have higher rates of labour induction, elective caesarean section, and small neonatal size for gestational age than pregnant women without multiple sclerosis, there is no evidence for an increased risk of other adverse neonatal outcomes.[22,23] Fatigue has been reported as a limiting factor for vaginal birth.[24] Epidural anaesthesia or mode of delivery are not associated with increased relapse rate in the post-partum period.[25]

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Risk of multiple sclerosis in offspring

The potential risk of inheriting multiple sclerosis is a commonly reported concern.[26] The age-adjusted risk of multiple sclerosis in offspring lies between 2·0% and 3·5%, and up to 20·0% if both parents are affected.[27] Although this risk is about 20-times to 30-times greater than the risk in the general population, it is much lower than would be expected with a monogenic Mendelian disorder. Therefore, people with multiple sclerosis should be reassured that there is a low risk of multiple sclerosis in their children. Avoidance of potentially modifiable risk factors of multiple sclerosis in offspring should be discussed.

Disease course around pregnancy

Short-term risk and predictors of relapse

The landmark Pregnancy in Multiple Sclerosis (PRIMS) study showed that the annualised relapse rate decreased from 0·7 in the 12 months before conception to 0·2 in the third trimester of pregnancy, then increased to 1·2 in the first 3 months post partum, with about one-third of women relapsing during this period.[2] This protective effect of the immunotolerant state of pregnancy, followed by an increase in relapse activity post partum, has been replicated in many other studies.[5,6] Possibly due to improvements in sensitivity and earlier diagnosis of multiple sclerosis, and changing use of DMTs, the relapse rate seems to have progressively decreased over time.[5,6,28]

In modern cohorts of women with multiple sclerosis, the relapse risk in untreated women, or in women treated with first-line therapies, is low during pregnancy and remains relatively low post partum for term or preterm pregnancies (annualised relapse rate 0·47–0·51), with only 14% of women reported to relapse in the first 3 months following delivery in one cohort of 1998 pregnancies.[5,28] However, even in the absence of clinical relapses, over 50% of women show new MRI activity in the first year post partum.[29–32] In modern cohorts, relapse activity in the year before conception, younger patient age (less than 35 years), and discontinuation of natalizumab and fingolimod before pregnancy are predictors of relapses during pregnancy.[5,33] Post-partum disease activity has been associated with pre-pregnancy disease activity (eg, relapses and MRI) and severity (higher Expanded Disability Status Scale [EDSS] scores), relapses during pregnancy, and preconception withdrawal of highly effective therapies.[5,29,33–35]

The withdrawal of sequestering and cell-trafficking DMTs (eg, natalizumab, fingolimod, and possibly other S1P receptor modulators) before or during pregnancy is associated with a particularly high risk of pregnancy-related relapse.[3–5,33,36] In a study of 274 pregnant women, the risk of severe relapse-related disability after natalizumab withdrawal was around 10% (29 of 274 women), and 1% (3 of 274) of women had catastrophic relapses resulting in an EDSS score of more than 8·5.[4] This relapse risk confers a substantial risk of long-term disability, and there are reports of maternal mortality in the context of drug withdrawal for pregnancy.[37] Continuing natalizumab into pregnancy can reduce this risk. The use of natalizumab during pregnancy is associated with a 24% reduction in the risk of relapse during pregnancy compared with discontinuation, and its use beyond the first trimester normalised rate of relapses during pregnancy to similar rates reported with use of low-efficacy DMTs before conception.[5] The use of depleting agents before pregnancy has also shown promising results of well controlled disease activity without rebound, even when treatment was paused during pregnancy.[34,38–41]

Although still largely understudied, disease activity after spontaneously or electively terminated pregnancies and stillbirths is approximately 10%.[5] Preconception relapse activity,[5,42] preconception gadolinium-enhancing T1 lesions, and elective terminations[42] are associated with an increased relapse risk following pregnancy loss.

The effects of breastfeeding and DMT use on post-partum relapse risk and disability

Observational studies on the effect of breastfeeding on post-partum relapse activity have shown variable findings; however, a meta-analysis suggested a protective effect.[43] Confounders include heterogeneity in study design and breastfeeding practices, as well as reverse causality.

Surprisingly few data are available on the effect of early DMT resumption on post-partum relapse risk. Logically, prompt re-initiation of DMT should reduce relapses through the course of the post-partum year. Unfortunately, a therapeutic lag exists for many medications,[44] so reducing the high relapse risk in the first 3 months post partum can be challenging.

There are currently insufficient data to understand whether continuing first-line injecta ble DMT during pregnancy reduces this relapse risk; data are likely to emerge as an increasing number of women continue these medications during pregnancy. The continuation of natalizumab throughout pregnancy and the post-partum period seems promising, but more data on the optimal timing of natalizumab administration during pregnancy in terms of risk–benefit balance are needed. The use of induction treatments with long-lasting benefit, such as alemtuzumab[41] and cladribine,[45] or long-acting anti-CD20 treatments, before pregnancy remains an option. Pregnancy-related relapses were rare in published cohort studies including approximately 220 pregnant women treated with anti-CD20 therapies, in whom the last infusion was generally given before pregnancy (approximately 80% [n=180] within 6 months of conception) but with some cases of accidental first trimester exposure (in less than 10%).[29,34,38,40] However, even with potent immunomodulators (eg, alemtuzumab), the absolute risk of relapse post partum is higher than the risk before pregnancy.[41]

Three DMT classes are officially approved for use during breastfeeding in Europe: interferon beta preparations, glatiramer acetate, and ofatumumab. Research

	Labelling*	First trimester exposure†	Exposure throughout pregnancy†	Rebound risk during pregnancy	Vaccinations‡[52]	Recommendations
DMTs						
Interferon betas (subcutaneous or intramuscular)	EMA: can be considered during pregnancy; FDA: no clear relationship with congenital malformations in humans [53-56]	No association with negative pregnancy outcomes in >2500 women[57,58]	No association with negative pregnancy outcomes in <100 women[57,59]	None[5]	All allowed in mother; no warning in exposed neonates	Do not stop before conception; discuss continuing during pregnancy or stopping at positive pregnancy test; premedication with ibuprofen should not be taken after 28 weeks of gestation due to premature closure of the ductus arteriosus; alternative is paracetamol
Glatiramer acetate (subcutaneous)	EMA: avoid in pregnancy unless benefit outweighs risk to fetus; FDA: insufficient data in humans to conclude risk of miscarriage or birth defects[60,61]	No association with negative pregnancy outcomes in >2500 women[62,63]	No association with negative pregnancy outcomes in >100 women[64-66]	None[5]	All allowed in mother; no warning in exposed neonates	Do not stop before conception; discuss continuing during pregnancy or stopping at positive pregnancy test
Dimethyl fumarate and diroximel fumarate§ (oral)	EMA: not recommended in pregnancy, use only if clearly needed and if benefit justifies potential risk to fetus; FDA: might cause fetal harm, but no adequate human data[67,68]	No association with negative pregnancy outcomes in >450 women[69,70]	Only single cases	None[5]	Withhold live vaccines in mother if low absolute lymphocyte count; exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop at positive pregnancy test
Teriflunomide (oral)	EMA and FDA: contraindicated in pregnancy; FDA: men with a desire to have children should stop and ensure concentration in blood <0·02 mg/L; EMA: no warning for men[71,72]	Spontaneous abortion risk 21·2%, but no increased congenital abnormality rate in 222 pregnancies;[73,74] pharmacovigilance and registry studies have not suggested a negative effect on the neonate with paternal exposure[73,75]	No data or only individual case reports	Case reports outside pregnancy[76]	Avoid live vaccines in mother; no warning in exposed neonates	Stop 24 months before conception; Alternative is accelerated elimination procedure with cholestyramine (ensure concentration <0·02 mg/L), also recommended in cases of unintended pregnancy exposure; men should be counselled regarding regulatory advice and existing data, and decisions taken based on personal risk–benefit ratio
S1P receptor modulators (oral)	EMA and FDA: contraindicated in pregnancy; FDA: warning for severe increase in disability after stopping	Suspected increased risk of congenital abnormalities (based on data for fingolimod due to expected class effect)	Only single cases	Present for fingolimod,[5,37] and possible but no data for other S1P receptor modulators	Avoid live vaccines in mother; no warning in exposed neonates but exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop before conception; replace with alternate DMT to decrease rebound risk such as a depleting therapy (anti-CD20 mAb or cladribine) or natalizumab
Fingolimod (oral)	EMA and FDA: contraindicated in pregnancy; FDA: warning for severe increase in disability after stopping[77,78]	Two times increased risk of congenital abnormalities suspected in at least a subset of studies (>800 pregnancies)[79]	Only single cases	Present[5,37]	Avoid live vaccines in mother; no warning in exposed neonates but exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop ≥2 months before conception
Ozanimod (oral)	EMA and FDA: contraindicated in pregnancy; FDA: warning for severe increase in disability after stopping[80,81]	No known negative outcomes (60 pregnancies[82])**	No data	Possible based on class effect but no data	Avoid live vaccines in mother; no warning in exposed neonates but exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop ≥3 months before conception
Siponimod (oral)	EMA and FDA: contraindicated in pregnancy; FDA: warning for severe increase in disability after stopping[83,84]	No data	No data	Possible based on class effect but no data	Avoid live vaccines in mother; no warning in exposed neonates but exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop ≥10 days before conception

(Table 1 continues on next page)

	Labelling*	First trimester exposure†	Exposure throughout pregnancy†	Rebound risk during pregnancy	Vaccinations‡[52]	Recommendations
(Continued from previous page)						
Ponesimod (oral)	EMA and FDA: contraindicated in pregnancy; FDA: warning for severe increase in disability after stopping[85,86]	No data	No data	Possible based on class effect but no data	Avoid live vaccines in mother; no warning in exposed neonates but exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Stop ≥1 week before conception
Cladribine (oral)	EMA and FDA: contraindicated in pregnancy; if on hormonal contraceptive, add barrier method ≥4 weeks after last dose; men should use contraception for ≥6 months after last dose[87,88]	Potential risks cannot be excluded; 16 pregnancies during or within 6 months of cladribine: n=2 (13%) spontaneous abortion, n=10 (63%) elective termination, n=1 (6%) therapeutic termination[89]	No data	None	Avoid live vaccines in mother; exclude haematological abnormalities before live vaccines in rare cases of exposed neonates during pregnancy	Last dose ≥6 months before conception for women and men
Natalizumab (intravenous or subcutaneous)	EMA: should be used during pregnancy only if clearly needed, discontinuation should be considered once pregnant; FDA: no adequate studies in humans, only use in pregnancy if benefit justifies potential risk to fetus[90,91]	Probably no increased risk of spontaneous abortion or congenital abnormality in neonate among >500 pregnancies[92–94]	Haematological abnormalities in <60 neonates[95]	Present[4,5,96]	Avoid live vaccines in mother; consider postponing live vaccines in neonates exposed in third trimester	Preferred: stop at 30–34 weeks of gestation with extended interval dosing (6–8 weeks), resume 1–2 weeks post partum; conservative: stop in second trimester; test neonate for haematological abnormalities, lactate dehydrogenase, and bilirubin if exposure in second or third trimester; alternative approach: switch to depleting agent before pregnancy to decrease rebound risk, especially in JCV antibody positive patients at increased risk of PML
Anti-CD20 monoclonal antibodies	Avoid pregnancy for several months after last infusion or injection, with recommended timing by EMA and FDA varying by anti-CD20 agent	Increased risk of spontaneous abortion or congenital abnormality unlikely	Risk for reduced B-cell count in neonates is probable with exposure in pregnancy	None	Avoid live vaccines in mother; exclude low B-cell count before live vaccines in exposed neonates	Time last dose before pregnancy (as listed according to each specific anti-CD20 therapy); choose conservative or active approach based on individual risk-benefit-evaluation
Ocrelizumab (intravenous)	EMA: avoid pregnancy for 12 months after last infusion; FDA: avoid pregnancy for 6 months after last infusion[97,98]	No association with negative pregnancy outcomes in >250 pregnancies**;[40,99] stillbirths (four [2%]) probably reporting bias of retrospectively reported pregnancies	Reduced B-cell count in neonates and slightly increased risk of preterm births and reduced birthweight cannot be excluded <30 pregnancies**[40,99,100]	None	Avoid live vaccines in mother; exclude low B-cell count before live vaccines in exposed neonates	Conservative approach: wait 3 months after last infusion; active approach: pregnancy attempts in the next menstrual cycle after the infusion;¶ stop infusions during pregnancy unless critically needed
Rituximab (intravenous)	EMA and FDA: avoid pregnancy for 12 months after the last infusion[101,102]	No association with negative pregnancy outcomes in >200 pregnancies,[38–40] although 27% spontaneous abortions in one study, attributed to high rate of pre-existing infertility[38]	Cases in conditions other than multiple sclerosis with reduced B-cell count in neonates[39]	None	Avoid live vaccines in mother; exclude low B-cell count before live vaccines in exposed neonates	Conservative approach: wait 3 months after last infusion; active approach: pregnancy attempts in the next menstrual cycle after the infusion;¶ stop infusions during pregnancy unless critically needed
Ofatumumab (subcutaneous)	EMA and FDA: avoid pregnancy for 6 months after the last injection[103,104]	Few data (n=30 pregnancies) with no congenital anomalies reported in 17 livebirths**[105]	No data	None	Avoid live vaccines in mother; exclude low B-cell count before live vaccines in exposed neonates	Conservative approach: stop when trying to conceive; active approach: stop when pregnant|| (time monthly injection with menses to decrease chance of exposure in pregnancy)
Alemtuzumab (intravenous)	EMA and FDA: avoid pregnancy for 4 months after last infusion[106,107]	Elevated risk of spontaneous abortion (22%) cannot be excluded (n=233 pregnancies);[41] placental transfer of anti-thyroid antibodies and neonatal Graves' disease reported	No data	None	Avoid live vaccines in mother; exclude haematological abnormalities before live vaccines in exposed neonates	Last dose 4 months before conception; test for thyroid function monthly during pregnancy

(Table 1 continues on next page)

	Labelling*	First trimester exposure†	Exposure throughout pregnancy†	Rebound risk during pregnancy	Vaccinations‡[52]	Recommendations
(Continued from previous page)						
Relapse treatment						
High-dose corticosteroids	NA	Theoretical risk of cleft palate, but findings in humans are less consistent;[108,109] low birthweight[110]	Low birthweight,[110] neurodevelopmental outcome effects[111]	NA	Avoid live vaccines in mother during and for 4 weeks after steroids	If treatment needed, use prednisone, prednisolone, or methylprednisolone
Plasmapheresis or immunoadsorption	NA	Few data; risks similar to those in non-pregnant individuals;[112,113] possibly reduced birthweight	Few data; pregnancy does not appear to confer additional specific risks[112,113]	NA	Avoid live vaccines in mother	Can consider in cases of severe relapse not responsive to steroids

DMT=disease-modifying therapy. EMA=European Medicines Agency. FDA=US Food and Drug Administration. JCV=John Cunningham virus. PML=progressive multifocal leukoencephalopathy. NA=not applicable. *Refer to latest product monographs from the EMA and FDA. †Only the most recent and landmark studies are referenced; refer to a review published in 2021 for additional references.[114] ‡Live vaccines are not given during pregnancy. §We have assumed that safety data for diroximel fumarate will be similar to dimethyl fumarate because these drugs have the same active metabolite, but data are not yet available. ¶Expert opinion based on a half-life of 18 days for rituximab and 26 days for ocrelizumab, and no placental transfer in the first trimester. ||Expert opinion based on a half-life of 16 days for ofatumumab and no placental transfer in the first trimester. **The latest data for the following DMTs are only available in abstract format to date.

Table 1: **Multiple sclerosis treatment exposure during pregnancy, including our recommendations based on physiological considerations and our experience and expert interpretation of available data**

efforts are underway to collect crucial data on DMT transfer into breastmilk. Information regarding potential beneficial interactions between DMT resumption during breastfeeding and short-term relapse risk is scarce, but this will increase as safety data emerge and breastfeeding on therapy becomes more widespread.

An improved understanding of the effect of childbearing on short-term disability stratified by drug class are needed to counsel women appropriately. Women with active disease who withdraw from sequestering treatments are at greatest risk.[3–5,33] Despite varying results, the strongest predictors of short-term disability worsening post partum seem to be relapses during pregnancy and early post partum, and baseline disability,[5,46,47] highlighting the need for careful pregnancy management with regard to DMT use, withdrawal, and re-initiation.

Long-term outcomes

In one study including 2557 women with incident clinically isolated syndrome, pregnancy was shown to delay clinically isolated syndrome by more than 3 years.[48] Further work is required to replicate this observation, and to understand the underlying mechanisms. In a previous study of women with clinically isolated syndrome, pregnancy was not associated with time to reach clinically definite multiple sclerosis or an EDSS score of 3·0.[49] Pregnancy after the onset of multiple sclerosis was not associated with worse disability outcomes in the long term,[50] aside from the effects of suspending DMT. In another study, less than 6% of women had confirmed disability progression events in the first year post partum.[5] Although a study with longer follow-up showed higher rates of confirmed disability progression in pregnant women with multiple sclerosis (65 [28%] of 230 women) than in non-pregnant women with multiple sclerosis (22 [22%] of 102) over a mean follow-up of 6·5 years (SD 3·1), it must be noted that pregnant women were exposed only to first-line injectable treatments, limiting the current applicability of these findings.[51]

Approach to DMT before and during pregnancy

Recommendations for approaches to DMT use around and during pregnancy are given in table 1. Fingolimod and natalizumab show the tensions inherent in ensuring both fetal and maternal safety. Although S1P receptor modulators are contraindicated during pregnancy due to potential teratogenicity, the risk of potentially fatal rebound of inflammatory activity has been reported with discontinuation of fingolimod (panel).[3,5,37] Strategies for the management of unplanned pregnancies in women receiving potentially teratogenic DMTs are highlighted in the panel. Natalizumab also has substantial rebound risk, although unlike fingolimod it is probably not teratogenic. Given the risk of severe rebound in pregnant women, natalizumab should not be discontinued before pregnancy or in the first trimester, but instead should be

Panel: **Case study of a woman with multiple sclerosis who became pregnant**

A 25-year-old woman was diagnosed with relapsing remitting multiple sclerosis by a multiple sclerosis specialist after several relapses with incomplete recovery and a high burden of demyelinating lesions on MRI. Her multiple sclerosis was well controlled on fingolimod for several years. At age 31 years, she decided to plan for pregnancy. She read that fingolimod should be stopped at least 2 months before attempting conception, so she stopped treatment and started prenatal vitamins. 2 months later, she stopped the oral contraceptive and began conception attempts.

3 months after stopping fingolimod, she developed new horizontal binocular diplopia and gait ataxia that worsened over 5 days. Brain MRI showed innumerable new and enhancing lesions. These clinical and radiological findings indicated a severe rebound attack due to cessation of fingolimod. Fingolimod was resumed and she used barrier protection for contraception. She unexpectedly became pregnant while on fingolimod.

Fingolimod was stopped but, to avoid another rebound attack, she was started on natalizumab, despite positive JCV antibody status, at extended interval dosing every 8 weeks, with the last infusion at 34 weeks of gestation. She delivered a healthy infant at 39 weeks of gestation, and the neonate had mild anaemia and thrombocytopenia that self-resolved. She resumed natalizumab 2 weeks post partum while breastfeeding. Due to JCV antibody seropositivity with rising index, she was transitioned to ocrelizumab at 3 months post partum, which she continued while breastfeeding. She did not have a post-partum relapse, but unfortunately was left with gait ataxia requiring a cane from her pre-pregnancy rebound relapse related to fingolimod cessation. Her infant had typical growth, development, and no clinically significant infections over the first 18 months of life.

Key points

- Discuss regularly if family planning is a consideration and adjust medications before pregnancy if necessary.
- Before attempting conception, teriflunomide and S1P receptor modulators should be stopped. Teriflunomide must be actively eliminated by cholestyramine or charcoal, otherwise it will remain in the body for up to 2 years as a result of enterohepatic circulation. Patients of both sexes on cladribine should be counselled not to attempt pregnancy until at least 6 months after the last tablet. In case of accidental exposure, organ screening ultrasonography and referral to a maternal–fetal medicine expert are recommended.
- If stopping a disease-modifying therapy with risk of rebound before conception, cell-depleting agents, such as anti-CD20 therapies (eg, ocrelizumab, rituximab, or ofatumumab) or induction treatments (eg, cladribine or alemtuzumab) can be used and timed before conception. Natalizumab can also be used but should be continued during pregnancy due to its risks of rebound at discontinuation.
- Rituximab could be used off-label in patients with highly active disease, particularly in low-income and middle-income countries if approved disease-modifying therapies are not available.
- In the case of accidental pregnancy while on S1P receptor modulators and in women with a previous history of rebound, consider switching to natalizumab during pregnancy to prevent rebound (with extended interval dosing).
- If natalizumab is used during pregnancy, the neonate should be checked for blood count abnormalities at birth and live-attenuated vaccinations should be postponed.
- Women with multiple sclerosis should follow the same delivery and anaesthesia recommendations as women without multiple sclerosis.
- Women with multiple sclerosis can generally breastfeed if desired, while on some disease-modifying therapies:
  - Monoclonal antibody therapies, including anti-CD20 therapies and natalizumab, have emerging safety data for use while breastfeeding, and are suggested for women at increased risk of post-partum relapses.
  - Breastfeeding while on interferon beta and glatiramer acetate is also safe.

continued at extended interval dosing (6–8 weeks) until the third trimester (30–34 weeks of gestation) with early reintroduction post partum, based on available data and our experience.[95]

Newer drugs, such as ocrelizumab, have restrictive pregnancy labels in both the EU (contraception should be used for 12 months after the last infusion of ocrelizumab) and in the USA (contraception should be used for 6 months after the last infusion of ocrelizumab), despite reassuring safety data for use closer to pregnancy in humans, including in the 3–6 months before conception,[29,34,38,40] leading to unnecessary concerns around planning pregnancy.[7] The use of cell-depleting medications, such as cladribine[45] or alemtuzumab,[41] and particularly anti-CD20 monoclonal antibodies for pregnancy planning is gaining traction, both to serve as a bridge therapy for women who are discontinuing natalizumab and S1P receptor modulators, and more generally to stabilise disease in patients with active multiple sclerosis. Overall, a low rate of relapses has been described in women who received anti-CD20 therapies within 3 months, or even 6 months, before conception,[29,38,40,115] including in women transitioning from fingolimod or natalizumab before pregnancy. Based on available data and our experience, we suggest targeting the last dose of anti-CD20 therapies shortly before pregnancy, but ideally not during pregnancy itself.

Molecular size influences drug safety during pregnancy. Small molecules (mostly oral medications) can cross the placental barrier easily at any timepoint, whereas the placenta is a mechanical barrier for larger molecules (eg, injectables or monoclonal antibodies). Oral drugs with potential teratogenicity must be stopped before pregnancy. Specific active transport mechanisms via fragment crystallizable receptors allow monoclonal antibodies to cross the placental barrier from the second trimester of pregnancy. Therefore, teratogenicity related to early exposure is highly unlikely but biological effects, such as haematological or immunological changes, in neonates exposed to these agents through maternal treatment in mid-pregnancy or late pregnancy can be seen.[39,40,95] Therefore, we recommend checking total lymphocyte and B-cell counts at birth in infants with anti-CD20 therapy exposure during the second or the third trimester of pregnancy. In case of neonatal lymphopenia or low B-cell count, live vaccinations, such as BCG and rotavirus, should be postponed until normalisation of B cells. Natalizumab exposure in utero during the third trimester can cause reversible anaemia and thrombocytopenia in the neonate, which should be evaluated and managed with the assistance of paediatricians, and postponing live vaccines in neonates with third trimester exposure should be considered.[95]

Autologous haematopoietic stem-cell transplantation is increasingly used for the treatment of multiple sclerosis at an earlier stage in the disease course than when initially trialled. BEAM (comprising carmustine, etoposide, cytarabine, and melphalan) and cyclophosphamide-containing conditioning regimens are anticipated to reduce fertility. Patients should be counselled about this risk of reduced fertility, with consideration for referral to a fertility specialist for egg harvesting or sperm collection and cryopreservation before treatment initiation. Spontaneous conceptions, without the need for fertility treatment, have been reported following autologous haemopoietic stem-cell transplantation in women and in the female partners of treated men,[116] and further prospective data collection is required to accurately assess the effects of this procedure on fertility.

The competing fetal or neonatal risks of DMT exposure versus the maternal risks of treatment discontinuation must be balanced, incorporating evolving scientific knowledge (figure 1). Modern medical peripartum management must incorporate the best risk–benefit analysis for both mother and child, related to pregnancy planning and breastfeeding, including peripartum maternal treatment continuation, if necessary. During the past decade, national and international pregnancy registries, along with pharmacovigilance studies, have provided valuable data that have helped to facilitate this decision making, avoiding harmful therapeutic inertia and unnecessary treatment withdrawal. Recommendations based on our collective experience and expert interpretation of the most up-to-date available data are given in table 1 and figure 2.

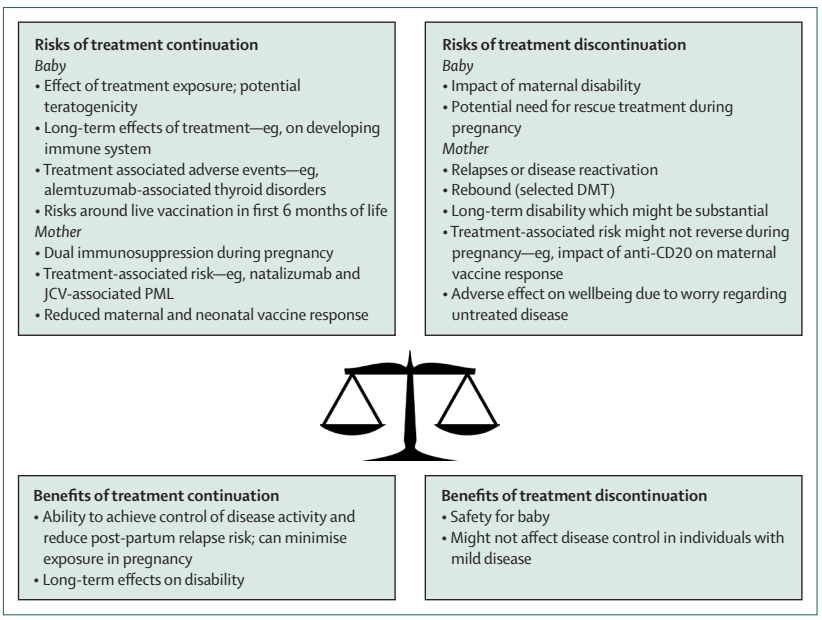

Figure 1: **Risks and benefits of DMTs for multiple sclerosis around pregnancy in mother and child**
DMT=disease-modifying therapy. JCV=John Cunningham virus. PML=progressive multifocal leukoencephalopathy.

Treatment of relapses during pregnancy

Relapse treatment during pregnancy needs to balance accelerated functional recovery with potential treatment-associated risk. Relapses with minor symptoms or not interfering with daily activities should not be treated. For relapses requiring treatment, non-fluorinated corticosteroids, including prednisone, prednisolone, and methylprednisolone, are preferred due to minimal placental transfer and short half-life.[117] Usually, 500–1000 mg methylprednisolone (or equivalent) daily for 3–5 days are recommended.

Animal studies have previously suggested a theoretical increase in the risk of cleft palate with corticosteroid exposure during the first trimester, but findings in humans are less consistent, and more recent data, within the past 10 years, do not show an association. An especially susceptible period for cleft palate development is at 8–11 weeks of gestation. Overall, glucocorticoids are considered to be low risk for use in pregnancy by The American College of Obstetricians and Gynecologists.[108,109] Corticosteroid exposure during pregnancy has also been associated with low birthweight[110] and effects on neurodevelopmental outcomes;[111] however, data are based on use of either non-selective or fluorinated corticosteroids.

Women who do not show a clinical response to steroids might benefit from plasma exchange or immunoadsorption during pregnancy. Although most reports consist of small cohorts and different treatment regimens, reassuringly, the safety profile of immunoadsorption and plasma exchange during pregnancy seems to be similar

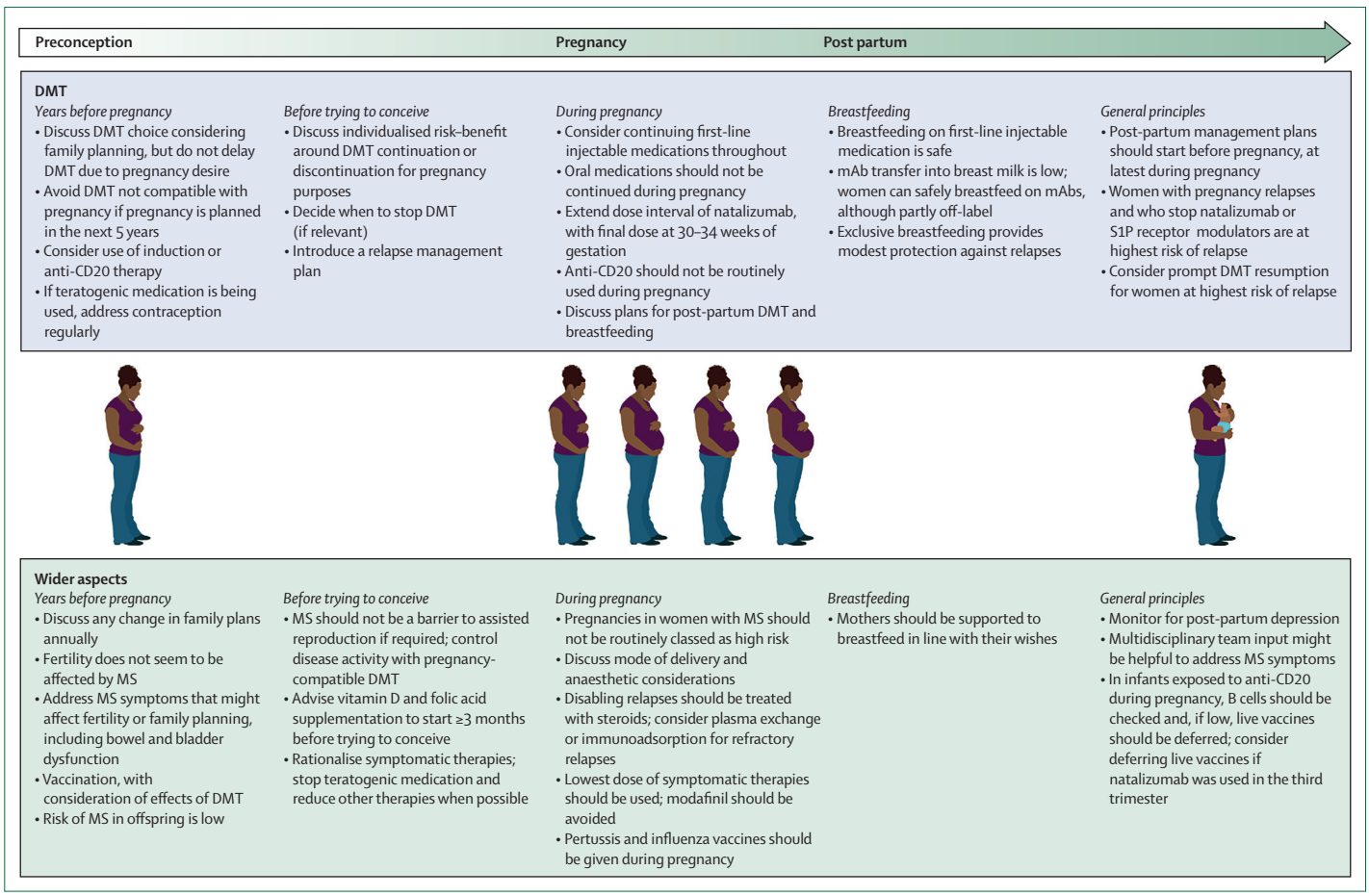

***Figure 2*: Recommendations for the management of women with multiple sclerosis before, during, and after pregnancy, based on our experience and expert interpretation of available data**
DMT=disease-modifying therapy. mAb=monoclonal antibody. MS=multiple sclerosis.

to that in non-pregnant individuals.[112,113] Intravenous immunoglobulin is not a conventional treatment for women with multiple sclerosis relapses and, due to an increased risk of thrombosis in pregnancy, is not recommended.

Post-partum management

Proactive planning to reduce the risk of post-partum disease activity should ideally start before pregnancy, especially in women with active multiple sclerosis. In these women, the preferred approach to reduce the risk of relapse both during pregnancy and post partum is treatment with either depleting agents, such as monoclonal antibodies directed against CD20, or induction treatments, such as cladribine or alemtuzumab (with the caveat of alemtuzumab being considered by many as a third-line option due to risks) in advance of pregnancy, or continuing natalizumab through the third trimester.

Given the health benefits of breastfeeding for both mother (including protection against breast cancer and potential protection against ovarian cancer and type 2 diabetes) and child (eg, reduction in infections and malocclusion, and probable reductions in long-term risk of obesity and diabetes),[118] women with multiple sclerosis should be supported to breastfeed if this is their goal. The European marketing authorisation for interferon betas changed in 2019 to state that these medications could be used during breastfeeding, with similar changes for glatiramer acetate in 2022. The marketing authorisation for ofatumumab states that it could be used during breastfeeding if clinically needed (table 2). This authorisation process will continue to evolve in light of accumulating evidence and class effects. Importantly, this change allows women to breastfeed while receiving DMT, and for physicians to prescribe according to the product label. The combination of breastfeeding and DMTs might further reduce the relapse risk over the post-partum year, but additional data are needed. For women at high risk of post-partum relapse, monoclonal antibody therapies are preferable over interferon beta or glatiramer acetate in our experience, given their higher efficacy and shorter therapeutic lag. For individuals not planning to breastfeed, DMT should be resumed early post partum.

Even where some DMTs are not formally approved, breastfeeding can be considered (table 2). Drug excretion in breastmilk is influenced by molecular weight, plasma protein binding, lipophilicity, and stage of lactogenesis, among other factors. The potential risk for breastfed infants is further shaped by oral bioavailability, medication toxicity, and the child's health status, and gastric pH, which changes as the infant matures. Relative infant dose (RID) can be calculated to determine the percentage of infant drug exposure through breastmilk

	Labelling*	Transfer into breastmilk	Infant exposure through breastfeeding	Recommendation for use during breastfeeding with mature breastmilk (≥2 weeks post partum)
DMTs				
Interferon betas (subcutaneous or intramuscular)	EMA: can be used during breastfeeding; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for interferon beta and any potential adverse effects on child from interferon beta or from underlying maternal condition[53-56]	Very low concentrations; case series (six women provided breastmilk) RID† 0·006% for interferon beta 1a;[119] case series (five women provided breastmilk) RID† 0·0054% for peginterferon beta 1a;[120] high molecular weight of about 19 kDa	Overall no side-effects and typical development and growth was reported in <100 infants[66,119,121]	Yes; no interval needed between injection and next breastfeeding. Premedication with ibuprofen or paracetamol allowed during breastfeeding
Glatiramer acetate (subcutaneous)	EMA: can be used during breastfeeding; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for glatiramer acetate and any potential adverse effects on infant from glatiramer acetate or from underlying maternal condition[60,61]	No data; presumably low or undetectable amount due to high molecular weight of about 10 kDa, although rapidly degraded	Overall typical development and growth reported in <100 infants[63,64,66,121,122]	Yes; no interval needed between injection and next breastfeeding
Dimethyl fumarate and diroximel fumarate (oral)	EMA: a decision must be made whether to discontinue breastfeeding or discontinue therapy; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for treatment and any potential adverse effects on infant or from underlying maternal condition[67,68]	Case report (two women provided breastmilk) dimethyl fumarate RID† 0·019% and 0·007%;[123] low molecular weight of 130 Da of active metabolite but transfer might be reduced by short half-life; no data for diroximel fumarate	No data	No, until more data available; if confirmed in further studies, breastfeeding might be considered
Teriflunomide (oral)	EMA and FDA: contraindicated during breastfeeding[71,72]	No data; presumably detectable amount due to low molecular weight of 270 Da and long half-life; detected in milk in animal studies	No data	No
S1P receptor modulators (oral)	EMA: should not breastfeed; FDA: developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on infant from treatment or from underlying maternal condition[77,78,80,81,83-86]	No data; presumably detectable amount due to low molecular weight of 307 Da (fingolimod), 404 Da (ozanimod), and moderate molecular weight of 1·1 kDa (siponimod) and long half-life; transfer might be reduced by high protein binding; detected in milk in animal studies	No data	No
Cladribine (oral)	EMA: breastfeeding contraindicated for 1 week after last dose; FDA: breastfeeding contraindicated for 10 days after last dose[87,88]	Case report (one woman provided breastmilk) RID† 3·06%, undetectable 2 days after last dose;[124] low molecular weight of 286 Da and low protein binding	No data	No
Natalizumab (intravenous or subcutaneous)	EMA: breastfeeding should be discontinued during treatment; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for natalizumab and any potential adverse effects on infant from natalizumab or from underlying maternal condition[90,91]	Low concentration, but unclear if accumulation could occur; case reports and series (total 20 women provided breastmilk); RID† 0·04–0·11% (11 women provided breastmilk);[125] maximum concentration 0·41 µg/mL (four women provided breastmilk);[126] RID† 0·50% (three women provided breastmilk), max concentration 0·14 µg/mL;[115] RID† 1·74–5·30% (one woman provided breastmilk);[127] no data on subcutaneous natalizumab	No effects on infant development and health attributable to breastmilk exposure in <20 infants;[115] no haematological abnormalities in two infants exposed only during lactation;[115] no natalizumab detected in blood of two infants after first infusion during lactation[115]	Yes; no interval needed between infusion and next breastfeeding
Ocrelizumab (intravenous)	EMA: women should be advised to discontinue breastfeeding during therapy; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for ocrelizumab and any potential adverse effects on infant from ocrelizumab or from underlying maternal condition[97,98]	Low or undetectable concentrations (23 women provided breastmilk); median RID† 0·28%, maximum RID 1·33%‡[128]	No adverse effects or overall typical infant development <1 year postpartum in 20 infants;[115,128,129]‡ infant B-cell count in normal range during lactation in two infants[115] and slightly decreased but recovered in one infant[130]‡	Yes; wait ≥4 h between pre-infusion antihistamines before next breastfeeding

(Table 2 continues on next page)

	Labelling*	Transfer into breastmilk	Infant exposure through breastfeeding	Recommendation for use during breastfeeding with mature breastmilk (≥2 weeks postpartum)
(Continued from previous page)				
Rituximab (intravenous)	EMA: breastfeeding is not recommended while being treated and optimally for 12 months following rituximab treatment; FDA: advise not to breastfeed during treatment and for 6 months after last dose[101,102]	Low concentrations; case reports and series (total 17 women provided breastmilk); RID† <0·40% (nine women provided breastmilk);[131] RID† <0·01% (one woman provided breastmilk);[132] RID† <0·3% (six women provided breastmilk)[133]	Overall typical growth and development and no concerns in ten infants;[115,131,132] normal B-cell count during lactation in eight infants;[115,133] Rituximab not detectable in one infant during lactation,[132] concentration <0·01 µg/mL in six infants[133]	Yes; wait ≥4 h between pre-infusion antihistamines before next breastfeeding
Ofatumumab (subcutaneous)	EMA: excretion of IgG antibodies in milk occurs during the first few days after birth, which decreases to low concentrations soon afterwards. A risk to the child cannot be excluded during this short period. Afterwards, ofatumumab could be used during breastfeeding if clinically needed. If the patient was treated with ofatumumab up to the last few months of pregnancy, breastfeeding can be started immediately after birth; FDA: the developmental and health benefits of breastfeeding should be considered along with mother's clinical need for ofatumumab and any potential adverse effects on infant from ofatumumab or from underlying maternal condition[103,104]	No data; presumably low or undetectable amount due to high molecular weight of >146 kDa and lower dose compared with other monoclonal antibodies	No data	Yes; no interval needed between injection and next breastfeeding
Alemtuzumab (intravenous)	EMA: breastfeeding should be discontinued during each course of treatment and for 4 months following the last infusion; however, benefits of conferred immunity through breastmilk might outweigh the risks of potential exposure to alemtuzumab for the infant; FDA: developmental and health benefits of breastfeeding should be considered along with mother's clinical need for alemtuzumab and any potential adverse effects on the child from alemtuzumab or from underlying maternal condition[106,107]	No data; presumably low but detectable amount comparable with other intravenous monoclonal antibodies; high molecular weight of >145 kDa; detected in milk in animal studies	No data	Probably acceptable; breastfeeding earlier than 4 months after the last infusion possible
Relapse treatment				
High-dose corticosteroids	NA	Methylprednisolone case reports: RID† <1·5%; pausing breastfeeding for 2–4 h after infusion reduces concentration in breastmilk[134]	No short-term adverse effects of pulse steroids on breastfeeding infants over 6–24 months of follow-up[134]	Acceptable, as exposure timeframe is brief in case of relapse treatment and can be reduced by pausing breastfeeding for 2–4 h
Plasmapheresis or immunoadsorption	NA	NA	Data are scarce, but no adverse effects reported[112,113]	Probably acceptable

DMT=disease-modifying therapy. EMA=European Medicines Agency. FDA=US Food and Drug Admini stration. RID=relative infant dose. NA=not applicable. *Refer to latest product monographs from the FDA and EMA. †RID estimates infant drug exposure per day (concentration in breastmilk multiplied by infant milk intake of 150 mL/kg per day) divided by (daily maternal dosage/kg); RID of <10% generally considered to be acceptable.[135] ‡The latest data for the following DMTs are only available in abstract format to date.

Table 2: **Multiple sclerosis treatment during lactation, including our recommendations based on physiological considerations and our experience and expert interpretation of available data**

compared with maternal dose, and a RID of less than 10% is generally considered to be safe for breastfeeding.[135] Although helpful, even if the RID is less than 10%, the potential for toxicity of individual drugs to the infant must still be considered, and a RID of less than 10% might not be adequate for highly toxic medications.

Monoclonal antibody therapies have low transfer to mature breastmilk (≥2 weeks post partum, after the colostrum and transitional milk phases), low expected oral bioavailability, and reassuring infant outcomes have been reported in more than 350 infants exposed to breastmilk of treated women.[131,136] Available data show promising results, with low breastmilk concentrations for natalizumab, rituximab, and ocrelizumab and no negative effects on infant growth, development, infections, or, when checked, lymphocyte levels.[129,131,132,133] A study investigating the effect of ocrelizumab on infant outcomes during breastfeeding is currently underway.[137]

Concentrations of cladribine (RID 3·06%)[124] and dimethyl fumarate (RID 0·007–0·019%)[123] in breastmilk are low. Nevertheless, the study populations are too small to recommend breastfeeding in women receiving these DMTs, and more data are required. Despite a RID of less than 10% for cladribine, potential toxicity is a concern.

High-dose corticosteroids, and if indicated plasma exchange or immunoadsorption, can be used to treat relapses during breastfeeding. There is little transfer of methylprednisolone to breastmilk (RID <1·5%), and

pausing breastfeeding for 2–4 h after an infusion to reduce the concentration in breastmilk can be considered.[134] Data do not support the use of intravenous immunoglobulin for prevention of post-partum relapses in women with multiple sclerosis.[138]

Up to 19% of women with multiple sclerosis develop post-partum depression,[139] with risk factors similar to those in the general population—eg, older age, first birth, and prepregnancy history of mood disorders.[140] Bowel and bladder dysfunction related to both multiple sclerosis or obstetric factors can arise, and pelvic floor physiotherapy should be encouraged. Input from a multidisciplinary team, including physiotherapy, occupational therapy, and social worker support, can assist with ambulatory function, spasticity, energy conservation, and adequate social and financial support during the post-partum period.

MRI during pregnancy and post partum

MRI is not routinely indicated during pregnancy, and its long-term predictive value post partum is unclear. If needed for new or worsening symptoms of multiple sclerosis, MRI can be performed during each trimester of pregnancy without increasing the risk of adverse pregnancy outcomes, including congenital anomalies.[141] Gadolinium-based contrast agents have been associated with a rare risk of stillbirth, neonatal death, or inflammatory skin disorders in one study, and should be used during pregnancy only if critically needed.[141,142] In the post-partum period, breastfeeding is compatible with gadolinium-based contrast agents and can be continued without interruption due to the low amount excreted in breastmilk.[142]

Symptomatic treatments during pregnancy and post partum

There is an absence of data on the safety of symptomatic therapies in pregnancy and during breastfeeding. There should be careful individualised decision making as to whether medication is required, and use of polypharmacotherapy should be minimised. If needed, women should be promptly referred for physiotherapy and psychological therapies to complement medication.

Pregnancy itself poses a risk of perinatal depression, and there seems to be an increased risk of peripartum depression in parents with multiple sclerosis.[139,143] If the benefit of continuing antidepressants outweighs potential risks, continuing medication during pregnancy and breastfeeding is justified. If possible, selective serotonin reuptake inhibitors (SSRIs) with the largest body of evidence on safety in pregnancy, such as sertraline or citalopram, should be considered. Women who are stable on antidepressants should have careful consideration of risks and benefits before switching. In neonates exposed to an SSRI during pregnancy, poor neonatal adaption, including hyperexcitability in the first 2 weeks of life, might be seen in up to 20–30% of infants.[144]

When antiepileptic drugs are needed, the lowest dose and least teratogenic medication should be used. Existing data on baclofen are scarce; however, an increased risk of congenital malformations was seen in one study, and there is a risk of neonatal withdrawal.[145] Tizanidine shows toxicity in animal studies.[146] Benzodiazepines are not associated with congenital malformations, but neonatal withdrawal is a risk when they are used throughout pregnancy. Modafinil is associated with an increased risk of congenital malformations and should be avoided in pregnancy.[147]

Family planning in low-income or middle-income countries

Few studies have investigated multiple sclerosis and pregnancy in low-income and middle-income settings. Access to health-care services can be poor and differs by country, with some countries having substantial out-of-pocket costs for health care. DMT availability and affordability differ in resource-limited settings, with some countries able to access only platform self-injectable DMTs.[148] Rituximab could be an affordable option in some resource-limited settings. Cultural differences, including traditional roles of women, also vary between countries, which might affect choices about prioritising the health of the child over that of the mother, even though maternal health is important to support fetal health. Maternal morbidity and mortality surrounding pregnancy differ between countries,[149] and addressing general obstetric care needs alongside multiple sclerosis care is crucial to improve the health of pregnant women with multiple sclerosis in resource-limited settings.

Considerations for men with multiple sclerosis

Sexual dysfunction remains underdiagnosed and undertreated, and can lead to infertility or reduced fertility in men. Around half of men with multiple sclerosis describe erectile and ejaculatory dysfunction, or reduced libido.[150] Medications, such as benzodiazepines, SSRIs, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants, might result in hyperprolactinaemia, potentially leading to hypogonadotropic hypogonadism and reduced testosterone concentrations.

Whether DMT exposure in men around conception can lead to reproductive toxicity remains unanswered. Potential mechanisms by which this toxicity could manifest include the interference with miosis within sperm, the presence of a drug in seminal fluid, and factors affecting gene expression, genomic imprinting, or DNA methylation.[151] Cladribine could affect male reproduction via its effect on DNA synthesis. Men are advised to not have children until at least 6 months following treatment completion, although real-world data are scarce.[89] Pharmacovigilance and registry studies have not suggested any negative effects of teriflunomide on neonatal outcomes, despite warnings on the US FDA label.[73,75] There are no label restrictions for other standard

Search strategy and selection criteria

We searched PubMed for relevant articles published in English, using search terms related to multiple sclerosis and family planning. The full list of search terms is included in the appendix (pp 1–2). We focused primarily on articles published from Jan 1, 2012, to Aug 29, 2022, but earlier pivotal studies were also considered. Studies relevant to clinical issues related to family planning in multiple sclerosis were included, and we focused on original research. Case reports were included only if data for a particular topic were limited to single cases.

See Online for appendix

approved DMTs for men with respect to pregnancy, including for S1P receptor modulators.

Conclusions and future directions

Multiple sclerosis often begins during key reproductive years, and counsellings on family planning should begin early. Importantly, multiple sclerosis does not seem to adversely influence fertility or birth outcomes. Inflammatory disease activity tends to decrease during pregnancy but increase post partum, with lower disease activity observed in modern cohorts of pregnant women either not receiving treatment or receiving platform first-line therapies than previously reported. Modern cohorts show high risks of in-pregnancy relapse and disability in women stopping S1P receptor modulators or natalizumab before conception, whereas anti-CD20 therapies continued until shortly before pregnancy, induction treatments before pregnancy, and the continuation of natalizumab during pregnancy, seem to result in well-controlled disease. Data on the safety of some DMTs during breastfeeding are emerging.

Given heterogeneity in multiple sclerosis, personalised care is important. Clinicians and patients must balance potential risks to the fetus or neonate from drug exposure during pregnancy and breastfeeding with maternal risks of treatment discontinuation or the decision not to re-initiate therapy post partum. For women with active disease, DMT use is important to avoid accumulation of demyelinating lesions and irreversible disability due to relapses during pregnancy and in the post-partum period. Multiple sclerosis should not be undertreated due to pregnancy desire and, with appropriate planning, most women with multiple sclerosis are able to safely have children. Understanding predictors of relapse activity during pregnancy and in the post-partum period is an unmet need. More data are also needed to confirm whether factors associated with peripartum relapse can be reduced by judicious use of DMTs before conception and after delivery. The evaluation of re-initiation of effective DMTs with short therapeutic lag early post partum also requires further study. As new DMTs emerge, ongoing collection of safety data on pregnancy exposure and lactation are required. Despite these challenges, treating multiple sclerosis through the pregnancy and post-partum period is potentially one of the most rewarding aspects of treating people with multiple sclerosis. The emergence of telemedicine could improve access to care by specialists with expertise in pregnancy and multiple sclerosis.

Contributors

KH designed the Review. KMK and RD assisted with design of the Review. KH, KMK, and RD submitted the final draft of the manuscript. All authors conducted literature searches, drafted and edited the manuscript, and approved the final version for publication.

Declaration of interests

KMK has received grants from the MS Society of Canada; speaking or consulting fees from Biogen, EMD Serono, Novartis, and Roche; and is an advisory board member for Biogen, Novartis, and Roche, outside the submitted work. RD has received payments to her institution, including grants from Biogen, Merck, Celgene, National MS Society, MS Society UK, Horne Family Trust, and the BMA Foundation; honoraria from Biogen, Janssen, Merck, Novartis, Roche, Sanofi, and Teva; participated on an advisory board for Biogen, Janssen, Merck, Novartis, and Roche; and received support for attending meetings or travel from Biogen, Janssen, Merck, Novartis, Roche, and Sanofi, outside the submitted work. MPA received grants for a sponsored statistician from Merck; consulting fees from Almirall, Bayer Schering Pharma, Biogen-Idec, Sanofi Genzyme, Merck-Serono, Novartis, and Roche; honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Merck-Serono, Novartis, Roche, and Sanofi-Genzyme; participated on the data safety and monitoring board or advisory board for Merck, Novartis, Roche, and Sanofi Genzyme; and reports a leadership role as president of The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), outside the submitted work. RB received investigator-initiated grants from Biogen, Novartis, and F Hoffman LaRoche, and sponsored grants from F Hoffman LaRoche; consulting fees from Alexion, Biogen, EMD Serono, Novartis, F Hoffman Laroche, Genzyme Sanofi, TG Therapeutics, and Janssen. AIC received speaker's honoraria from Bayer Healthcare; and support for attending meetings from Teva, outside the submitted work. MM received grants from the Danish MS Society; consulting fees from Merck, Sanofi, Roche, and Novartis; payment or honoraria from Merck, Sanofi, Roche, Novartis, Biogen, and Bristol Myers Squibb; and participated on the data safety and monitoring board or advisory board for Merck, Sanofi, Roche, Novartis, Biogen, and Bristol Myers Squibb, outside the submitted work. ST received speaker honoraria from Bayer Healthcare and Biogen GmbH, and manuscript writing assistance from Hexal AG, outside the submitted work. MT received grants for a sponsored statistician from Biogen; consulting fees from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Janssen, Merck-Serono, Novartis, Roche, Sanofi-Aventis, Viela Bio, and Teva Pharmaceuticals; honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Janssen, Merck-Serono, Novartis, Roche, Sanofi-Aventis, Viela Bio, and Teva Pharmaceuticals; and reports a leadership role as ECTRIMS vice president, outside the submitted work. SV has received payments to her institution including grants from Biogen, Janssen, Merck, Novartis, Roche, and Sanofi; consulting fees from Biogen, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, Roche, and Sanofi; honoraria from Biogen, Merck, Novartis, Roche, Sanofi, and Teva; participated on the data safety and monitoring board or advisory board for Biogen; support for attending meetings or travel from Biogen, Merck, Novartis, and Roche, outside the submitted work. KH received grants or contracts from Almirall, Biogen, Merck, Novartis, Sanofi Genzyme, Roche, and Teva; payment or honoraria from Almirall, Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Roche, Teva, Janssen, and Bristol-Myers Squibb; support for attending meetings or travel from Bayer, Biogen, Merck, Roche, Sanofi Genzyme, and Teva; participation on a data safety and monitoring board or advisory board from Biogen, Teva, Roche, Novartis, Jansen, and Merck, outside the submitted work. RA, YF, MH, VGJ, AA, VP declare no competing interests.

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