Neurol Ther (2023) 12:1–10
https://doi.org/10.1007/s40120-022-00421-0

COMMENTARY

Multiple Sclerosis in Pregnancy: A Commentary on Disease Modification and Symptomatic Drug Therapies

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Received: September 29, 2022 / Accepted: November 1, 2022 / Published online: November 28, 2022

ABSTRACT

Multiple sclerosis (MS) frequently affects women of childbearing age, and an increasing number of disease-modifying therapies are available. However, a consequence of this is that women and clinicians face complex shared decisions surrounding disease-modifying therapy use in pregnancy and postpartum. It has been suggested that there are both knowledge and communication gaps that need to be addressed in order to improve outcomes for women with MS desiring a pregnancy. Existing pregnancy studies are subject to limitations including selection bias and missing data; however, when these are combined with clinical expertise, consensus guidelines can be developed and used as a framework to support this complex decision-making process. This commentary paper aims to provide a practical and evidence-based overview of the safety of disease-modifying therapies and symptomatic drug therapies during pregnancy and breastfeeding, along with highlighting where insufficient data exist to guide practice.

PLAIN LANGUAGE SUMMARY

Multiple sclerosis is more common in women than men, and many women with multiple sclerosis have not completed their families when they are diagnosed. This means that they face complicated decisions around using disease-modifying therapies, many of which have limited evidence for use in pregnancy. Conversations between clinicians and women with multiple sclerosis around pregnancy do not always address all of the issues that women face, partly because not all of the needed information is available. Consensus guidelines have recently been developed, and both experience and opinion have been used to inform these. This paper provides a practical overview of the use of treatments for MS and its symptoms.

Keywords: Disease-modifying therapy; Multiple sclerosis; Pregnancy; Symptomatic treatment

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Key Summary Points

Multiple sclerosis is often diagnosed in women before they have completed their families.

Earlier use of disease-modifying therapies (DMT) is increasingly common, meaning that many women face complex decisions around balancing DMT use and family planning.

Consensus guidelines provide practical approaches based on available evidence and expert opinion, and these can be used to guide treatment around pregnancy.

Balancing risks of stopping DMT vs. continuing during pregnancy requires an individualized approach and discussion with women and their families.

Further studies are required to improve the evidence available to women and clinicians.

BACKGROUND

Multiple sclerosis (MS) more frequently affects women of childbearing age with male-to-female ratios of 2–3:1 in various studies [1]. Advancements in the number of disease-modifying therapies (DMTs) coupled with limited studies investigating the safety of these medications during pregnancy and breastfeeding result in women and clinicians facing complex shared decisions surrounding DMT use in pregnancy and postpartum. Increasingly, the importance of prompt initiation of DMT results in many women with MS having to navigate these challenging conversations prior to embarking on a pregnancy.

From a clinician's perspective, variation in treatment approaches around pregnancy amongst neurologists is based on a variety of factors, including perception of risk–benefit and DMT availability. It has been suggested that there are both knowledge and communication gaps that need to be addressed in order to improve outcomes for women with MS desiring a pregnancy [2]. From the perspective of women with MS, decisions surrounding DMT initiation can sometimes feel like "walking into the unknown" with fear and uncertainty accompanying these discussions [3].

While existing pregnancy studies are subject to limitations including selection bias and missing data, when these are combined with clinical expertise, consensus guidelines can be developed and used as a framework to support this complex decision-making process [4, 5]. This paper aims to provide a commentary and an overview of the safety of DMTs and symptomatic drug therapies during pregnancy and breastfeeding. We hope to address some of these knowledge gaps and subsequently empower women with MS hoping to embark on a pregnancy to make informed decisions on these medications.

Compliance with Ethics Statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PRECONCEPTION COUNSELING

Clinicians should have discussions regarding the possibility and wishes for pregnancy with every woman of childbearing potential who has been diagnosed with MS. These discussions should ideally take place as early as possible, as this has the potential to influence subsequent DMT choice. A period of disease stability should be aimed for prior to trying to conceive and this will be individual dependent with the use of high-effective therapies in some and the use of maintenance therapies in others. When switching therapies or allowing for washout periods, discussions with women planning pregnancies should be carried out in advance, with the aim of minimizing risks of relapse and potential fetal exposure to teratogens.

Women who are on symptomatic therapies should also be provided with individualized

advice on drugs that are safe to continue in pregnancy and breastfeeding. Prompt referrals to specialist mental health and physiotherapy services should be carried out where women are likely to benefit from such input.

Women should be advised that the majority of MS pregnancies result in a healthy baby and that the risk of relapse is the highest postpartum [6]. It appears that this risk can be partially mitigated by rapid resumption of DMT, exclusive breastfeeding, and control of disease activity prior to pregnancy. While most women do not relapse during pregnancy, long-term disability has been associated with relapses in the year prior to conception [7], further highlighting the importance of disease stabilization and treatment optimization in patients planning pregnancy.

SAFETY OF DISEASE-MODIFYING THERAPIES IN PREGNANCY AND BREASTFEEDING

Discussions surrounding DMT use in pregnancy and postpartum should be individualized to the woman's disease activity and severity alongside their views around treatment during pregnancy. It must be noted that not every woman requires treatment during pregnancy, and it may be that women with relatively mild disease stop DMTs during their pregnancy. Conversely, continuing DMT alongside minimizing any risk to the fetus is appropriate for women with more active disease. A summary of recommendations for DMTs pre-pregnancy, during pregnancy, and postpartum are displayed in Tables 1, 2, and 3.

First-Line Injectable Medications (Interferon Beta and Glatiramer Acetate)

First-line injectable medications (interferon beta and glatiramer acetate) are generally considered safe during pregnancy with benefits of breastfeeding on treatment outweighing risks [5, 8, 9]. An important point to note for those women that decide to stop this medication during pregnancy is that it can take 3–6 months to reach full efficacy when restarted.

Table 1 Recommendations for DMT use pre-pregnancy

DMTs potentially safe to continue until or close to conception	DMTs that require substantial wash-out periods pre-pregnancy
First-line injectable medications (interferon beta and glatiramer acetate) can be continued to the time of conception	Fingolimod and related drugs: Fingolimod must be stopped at least 2 months prior to trying to conceive (TTC); other related drugs should be stopped according to recommendations in SmpC
Dimethyl fumarate: Short half-life, and can be continued shortly prior to trying to conceive, or in some cases until conception occurs	Teriflunomide: Teratogenic, accelerated elimination recommended if unplanned pregnancy
Natalizumab: can be continued until conception; in these cases, the woman should plan to continue during pregnancy	*Induction therapies may allow for DMT-free pregnancy where people are not immediately planning pregnancy:*
Anti-CD20 monoclonal antibodies with 6-monthly dosing schedules (rituximab, ocrelizumab): can conceive 1–3 months after dose, if no pregnancy can have a further dose 6–9 months later	Alemtuzumab: Can conceive 4 months following treatment
	Cladribine: Teratogenic, avoid conception for 6 months following course in both males and females

Oral Medications

Oral medications such as dimethyl fumarate, fingolimod, siponimod, ponesimod, ozanimod, and teriflunomide are small molecules, meaning that fetal exposure occurs early in pregnancy along with subsequent transport across the placenta. This needs to be considered when prescribing these drugs prior to and/or during pregnancy.

Table 2 Recommendations for DMT use during pregnancy

DMTs potentially safe to continue during pregnancy	DMTs that should be avoided in pregnancy
First-line injectable medications (interferon beta and glatiramer acetate) no evidence of harm during pregnancy	Dimethyl fumarate: lack of safety data with few cases and should be stopped during pregnancy
Natalizumab can be continued with special considerations (increasing dosing interval, last dose no later than 34 weeks to minimize fetal exposure); in general, the risk of continuing is lower than the risk of relapse/rebound if this medication is withdrawn	Fingolimod and related drugs—Fingolimod is a known teratogen; safety studies on other S1P not yet completed, risk of class effect
Anti-CD20 (ocrelizumab, ofatumumab)—reserve use in pregnancy for those at highest risk, risk of low B-cell counts in neonates (need FBC monitoring), and specialist advice around vaccines in the infant	Teriflunomide—teratogenic in animals and contraindicated
	Cladribine: should not be used during pregnancy
	Alemtuzumab: should not be administered during pregnancy, if received dose preconception needs close monitoring with FBC (thrombocytopenia) and thyroid and autoimmune disease, consideration for irradiated blood products

Table 3 Recommendations for DMT during breastfeeding

DMTs potentially safe to continue during breastfeeding, or where breastfeeding can be temporarily suspended during DMT administration	DMTs where breastfeeding should be temporarily suspended during DMT administration, but where this may be feasible in established breastfeeding
First-line injectable medications (interferon beta and glatiramer acetate): Safe in breastfeeding with no transfer to the infant (Note: lack of clear evidence supporting reduction of postpartum relapse rate)	Cladribine: only detectable in breastmilk for a short time and can be advised to temporarily suspend breastfeeding during course and at least 7 days after last dose
Natalizumab: should be continued, transferred into breast milk but oral bioavailability negligible	Alemtuzumab: no safety data on breastfeeding, should be avoided during treatment, but given short duration of treatment may be possible to temporarily suspend breastfeeding where this has already been established
Anti-CD20 (ocrelizumab, ofatumumab): can be continued	

Dimethyl fumarate: Due to the short half-life of dimethyl fumarate, its active metabolite monomethyl fumarate is no longer detectable in the circulation within 24 h of stopping medication [10]. This allows the medication to be continued until conception, but it should be stopped during pregnancy, and individual risk-benefit discussions should take place around use in breastfeeding. Pregnancy registers have not demonstrated any increased risk of early pregnancy loss or congenital malformation with exposure early in pregnancy [11].

Fingolimod and other sphingosine-1-phosphatase inhibitors: Fingolimod is not recommended during pregnancy due to an increased risk of cardiovascular and musculoskeletal malformations, which is in accordance with its mechanism of action [12]. It is also contraindicated in breastfeeding. Women on fingolimod should use effective contraception during treatment and stop the medication at least 2 months prior to conception for an effective washout period. However, it must be noted that significant disease rebound has been described on fingolimod discontinuation, including for pregnancy purposes when fingolimod is stopped either prior to, or immediately following, confirmation of pregnancy [13, 14]. It may be

preferable for patients to switch to pregnancy-compatible DMT in order to reduce this risk, and this should be taken into account when starting DMT. This potential difficulty also highlights the importance of proactive discussions around pregnancy planning in all patients starting DMT of childbearing potential, regardless of their pregnancy plans in the immediate future.

Ponesimod, siponimod, and ozanimod belong to the same drug class of drug as fingolimod, and while they may be more selective, a similar class effect must be assumed in the absence of data to the contrary. To date, there are no data available regarding the use of these medications during pregnancy, although regulatory and registry studies are ongoing.

Teriflunomide: Teriflunomide should be avoided during pregnancy due to its teratogenicity in animal studies [10] and it is contraindicated during breastfeeding. Accelerated elimination is advised should unplanned pregnancy occur due to the extended half-life. Real-world evidence is limited at present, with only small numbers of women enrolled in pregnancy registers and limited evidence from real-world studies [15].

Monoclonal Antibodies with Continuous-Dosing Regimes

In general, monoclonal antibodies do not cross the placenta until the second trimester of pregnancy [16], meaning that congenital malformations are less likely. However, fetal exposure increasingly occurs as pregnancy progresses, meaning that neonates may have consequences in keeping with the mechanism of action of the antibody [16]. Due to the range of mechanisms of actions and dosing intervals, each monoclonal antibody should be considered separately.

Natalizumab: When taken in the third trimester of pregnancy, natalizumab has been linked to hematological complications, low birth weight, and increased hospital admissions in the infant's first year [17]. No increased risk of spontaneous abortion and congenital malformation has been found. An important factor to consider is disease reactivation in response to natalizumab withdrawal [18] both prior or during pregnancy, which has serious implications leading to the accumulation of permanent irreversible disability [19]. More recent data add support to the approach of continuing natalizumab during pregnancy with early treatment postpartum, rather than cessation prior to or following conception, as this appears to be associated with lower clinical and radiological MS disease activity in the post-partum period [20].

Individuals with highly active MS are therefore recommended to either switch to an alternative agent (ocrelizumab or alemtuzumab), which does not require dosing during pregnancy, or to continue the medication during pregnancy with extension of the dosing interval to 6–8 weeks with the last dose given before 34 weeks of gestation followed by prompt redosing following delivery [21].

Although natalizumab is transferred into breast milk and increasing amounts over time [22], it should not be discontinued while breastfeeding as the oral bioavailability is negligible [5].

Anti-CD20 therapies (ocrelizumab, ofatumumab, rituximab): ocrelizumab and rituximab with their biannual dosing schedules are favorable for pregnancy due to minimal fetal drug exposure. In women with more active MS, pregnancy may be attempted 1–3 months after rituximab or ocrelizumab as these drugs are usually eliminated at around 4 months and IgG does not cross the placenta until the second trimester. A further dose can be administered if women do not fall pregnant by 6–9 months after their initial dose. Planning pregnancy around ofatumumab is more complex given the monthly dosing schedule, particularly as prolonged efficacy in the absence of treatment during pregnancy cannot be assured.

In general, monoclonal antibodies including anti-CD20 therapies do not pass into breast milk at high concentration [23] once colostrum has cleared, and therefore breastfeeding is possible on these therapies, and within the SmPC for ofatumumab.

Women need to be advised that the data overall for anti-cd20 monoclonal antibodies are

limited with uncertainty around infection risk during the immunosuppressed state of pregnancy with risks of low B-cell counts in infants exposed to these medications, which is likely a class effect. Such infants should have full blood count monitoring and specialist input regarding the safety of live vaccines [24].

Induction Therapies: Cladribine and Alemtuzumab

The long-lasting therapeutic benefits for induction agents provide the potential for a DMT-free pregnancy provided women and their partners are prepared to wait before trying to conceive.

Women on cladribine should be advised to use dual contraceptive methods for 4 weeks post dose and not conceive for 6 months following a course. Men on cladribine should also take the same precautions. Conception following alemtuzumab can safely occur 4 months after treatment and if needed, further doses can be given after pregnancy due to the long-lasting benefit. Women who have taken alemtuzumab should be made aware of the importance of thyroid function and full blood count monitoring due to risks of unrecognized maternal thyroid disease or thrombocytopenia [5].

SAFETY OF SYMPTOMATIC THERAPIES IN PREGNANCY AND BREASTFEEDING

Although there have been numerous studies investigating the safety of DMTs during pregnancy and breastfeeding, research into symptomatic therapies is scarce with various limitations of the current literature such as confounding from maternal illness, small sample sizes, lack of standardization, and lack of control groups.

Depression

Women on selective serotonin reuptake inhibitors (SSRIs) should be promptly referred to teams with appropriate experience in mental health during pregnancy and postpartum. They should be counseled on the benefits of taking medication during pregnancy and the risks such as a possible increase in overall and cardiovascular birth defects in small studies (with no teratogenic effects), possible small increase in PPHN (small absolute risk overall of around 1%) and a small risk of PPH if used in the month before delivery [25, 26]. Other associations with low birth weight, ASD, and preterm birth have been conflicting, and possibly confounded by underlying maternal depression. Monitoring for withdrawal is important in the baby if used in the third trimester. For those women that decide to stop medication during this time period, a gradual tapering should be carried out. If appropriate, referral to psychological therapies such as cognitive behavioral therapy (CBT) should also be considered.

Some antidepressants such as amitriptyline and duloxetine may be used for the treatment of neuropathic pain. While the doses used for the treatment of pain are, in general, lower than those used for the treatment of mood disorders, any potential impact remains the same regardless of indication.

Pain

Agents to treat pain should be prescribed based on the type of pain experienced including simple analgesia such as paracetamol, codeine (if paracetamol is inadequate), and ibuprofen. Dihydrocodeine should be used instead during breastfeeding and ibuprofen should be avoided in the third trimester. Limited evidence for amitriptyline suggests that this is safe to continue during pregnancy and breastfeeding. With regards to carbamazepine, in cases where benefits outweigh risks, it can be continued at the lowest possible dose with supplementary high-dose folic acid to reduce neural tube defect risk. Women planning pregnancy should be advised regarding an increased risk of major malformations, neonatal complications, and neurodevelopmental impairment with the higher doses used in epilepsy [27]. Duloxetine, which can be used to treat mood disorders and pain, should not be routinely prescribed during

pregnancy due to limited safety data but can be taken during breastfeeding if required.

Gabapentin is preferable to pregabalin during pregnancy and breastfeeding with a slight increase in major malformations in women taking pregabalin in a large observational cohort study [28]. The study, however, has major limitations including the influence of data confounding due to lack of adequate control groups with an overall small increase in absolute risk. Women on gabapentin or pregabalin should also take high-dose folic acid. Where adequate pain control cannot be achieved with other agents, tramadol can be used during pregnancy and breastfeeding.

Spasticity

Baclofen should be used with caution due to a possible increased risk of congenital malformations [29]. Both fampridine and tizanidine should be avoided during pregnancy and breastfeeding due to lack of safety data. There are no studies specifically for Sativex but data extrapolated from cannabis use during pregnancy recommend against its use. Clonazepam and diazepam are both safe and compatible and women should be counselled on taking small doses for short amounts of time and advised against abrupt withdrawal of the medication.

Fatigue

Women taking amantadine and modafinil preconception for fatigue should be advised that both medications should not be continued during pregnancy and breastfeeding. There is a lack of safety information for amantadine and an increased risk of congenital malformations with modafinil use in the first trimester [30]. Zopiclone could be considered after careful discussion during pregnancy and breastfeeding.

Infections

Urinary tract infections (UTI) are common in people with MS, and are more frequent during pregnancy. Therefore, while any infection may occur during pregnancy, UTI are the most common reason for antibiotics in this group. Pregnant women should be made aware that they might experience a temporary worsening of their MS symptoms during any infection. Amoxicillin, co-amoxiclav, and cephalosporins are safe during pregnancy and breastfeeding. Nitrofurantoin may have an association with congenital malformations when prescribed in the first trimester, and so alternatives should be used during this time [31].

SAFETY OF INTRAVENOUS STEROIDS DURING PREGNANCY AND BREASTFEEDING

Relapses causing significant disability and reduction and mobility can be treated with intravenous methylprednisolone during pregnancy and postpartum after excluding an underlying infection. IVIG or plasma exchange can be considered as the second-line treatment for severe relapses that are not treated adequately with steroids. Historically, steroids have been associated with cleft palate abnormalities following early pregnancy exposure but this has been shown to be lower than that seen in previous studies [32]. A potential long-term risk of adverse neurodevelopmental outcomes has been proposed [33] but is biologically less likely with methylprednisolone. IVIG is also considered safe but a possible increased risk of thrombotic events needs to be considered [34]. Steroids are associated with impaired glucose tolerance, with potential for gestational diabetes [35], and both steroids and IVIG are associated with hypertension [36]; where these medications are administered during pregnancy women should be monitored appropriately, with early active treatment of any such adverse effect.

DISCUSSION

An individualized approach taking into account a pregnant woman's MS disease activity and symptom severity alongside their personal views and acceptability of risk to the fetus is paramount when making decisions on

continuation, cessation, and switching of drug therapies during pregnancy and breastfeeding. Detailed discussions should take place in preconception clinics with women and their families being provided with all available evidence in order to make an informed shared decision. Achieving disease stability prior to pregnancy is an important factor to consider.

More studies investigating the safety of DMT and symptomatic therapies during pregnancy and breastfeeding are required in order to strengthen the current evidence base for these medications, which would thereby facilitate more effective counseling regarding starting and stopping treatments. MS pregnancy registers provide a unique platform for collection of real-world data surrounding the choices women make regarding medications during pregnancy and postpartum along with an opportunity for prospective data collection on medications and pregnancy-related outcomes.

National and local pregnancy registers have been developed in a number of countries. One of the first to launch was the German MS Pregnancy Register [37], which has provided considerable data around the safety of various DMT in pregnancy. The French pregnancy register, which sits within a national disease register, has similarly provided considerable data to inform care [38]. Healthcare records and claims databases are also used to provide data around MS and pregnancy [39, 40]. The UK MS Pregnancy Register was launched in 2021 [41] and has currently recruited over 120 participants across the country. The overarching aim of the register is to gain information on the experience of pregnancy and postpartum period for women with MS. This patient-facing register involves women filling out questionnaires during pregnancy and the first year following birth with women with MS being involved in the questionnaire design ensuring that data captured is relevant to both women and clinicians involved in their care.

CONCLUSIONS

This paper provides an overview of the current evidence base for the safety of DMT and symptomatic treatments for MS during pregnancy and breastfeeding. There are various treatment options that allow women to achieve disease stability before, during, and after pregnancy, thereby reducing the risk of relapses and long-term disability. Timely preconception counseling with the pregnant individual at the core of the decision-making process is key to achieving optimal outcomes for the mother and fetus. Further studies targeting women with MS are needed to address current research gaps with data from large register-based studies providing a real-world alternative.

ACKNOWLEDGEMENTS

The authors would like to thank all of the people with MS who have provided time, opinions, and information to focus groups, PPI, and pregnancy registers. They have been key in highlighting knowledge gaps and the impact of these.

Funding. No funding or sponsorship was received for this study or publication of this article. This work was performed on the PNU, which is part funded by Barts Charity. The UK MS Pregnancy Register is supported by funding from the Horne Family Charitable Trust.

Author Contributions. PI drafted the manuscript with significant intellectual contribution from RD. All authors approved the manuscript for submission.

Disclosures. PI has no conflicts to declare. RD receives grant support from the UK MS Society, NMSS, Horne Family Charitable Trust, Biogen, Celgene, and Merck. She has received honoraria for advisory boards and/or educational activities from Biogen, Teva, Sanofi, Merck, Novartis, Janssen and Roche.

Compliance with Ethics Statement. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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