Article begins on page three of this document.

Title	Family planning and antenatal, perinatal and post partum care in multiple sclerosis: a review and update
-------	--

Authors:

	Title	First name	Mid inits	Last name	Postnom (eg, PhD) [3 only for publication]	Position1	Address1	Position2	Address2	Tel	Email
1	Asso c. Prof.	Anneke		Van Der Walt	PhD, MBChB, FRACP	Head, MS and Neuroophthalmology	1	Head, MS and Neuroophthalmology	2,3		anneke.vanderwalt@monash.edu
2	Dr.	Ai-Lan		Nguyen	MBBS, BMedSc, FRACP	Neurologist	2		4		a.nguyen99@gmail.com
3	Dr.	Vilija		Jokubaitis	PhD	Senior Research Fellow	1		2,3		vilija.jokubaitis@unimelb.edu.au
4											
5											

Number of corresponding author:	1
Number of alternative corresponding author:	

Addresses:

	Institution		City	State	Post Code	
1	Monash University		Melbourne	VIC	3004	
2	University of Melbourne		Melbourne	VIC	3010	
3	Alfred Health		Melbourne	VIC	3004	
4	Royal Melbourne Hospital		Melbourne	VIC	3050	
5						
6						

Postal address of first corresponding author (if different from the institutional address given above)	
--	--

Primary Keywords [Office use only]	Nervous system diseases; Women's health
Secondary keywords [Office use only]	Multiple sclerosis; Family planning; Pregnancy; Breastfeeding
Notes:	

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/MJA2.50113](#)

This article is protected by copyright. All rights reserved

Article details (press ctrl – 9 to enter details):

Article type	Narrative review
Blurb	For women with multiple sclerosis, assessment of fertility and disease characteristics using a multidisciplinary approach is required to ensure positive outcomes in mothers and children

Office use

<i>Ms. Number</i>	mja18.00055. R3
<i>Medical editor</i>	Francis Geronimo
<i>Medical editor email</i>	fgeronimo@mja.com.au
<i>Structural editor</i>	Laura Teruel
<i>Structural editor email</i>	lteruel@mja.com.au
<i>Section/Category</i>	Narrative review
<i>Strapheading</i>	Narrative review
<i>Substrap</i>	

Wiley – file data:

Filename for copyediting	van_mja18.00055_ms.docx
Accompanying graphics	None
Stock images	None
Appendices	None
Online first	01/04/19

Office use – history:

Event	Date
Original submission received	15/01/2018

Event	Date
Accept	26/11/2018

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	
Issue	
Vol	
DOI	10.5694/mja18.00055
Journal	The Medical Journal of Australia
Original article DOI (for response)	

Family planning,antenatal and post partum care in multiple sclerosis: a review and update

Summary

- Multiple sclerosis is more prevalent in women of childbearing age than in any other group. As a result, the impact of multiple sclerosis and its treatment on fertility, planned and unplanned pregnancies, post partum care and breastfeeding present unique challenges that need to be addressed in everyday clinical practice.
 - Given the increasing number of disease-modifying agents now available in Australia for the treatment of multiple sclerosis, there is a growing need for clinicians to provide their patients with appropriate counselling on family planning.
 - Providing better evidence regarding the relative risks and benefits of continuing therapy before, during and after pregnancy is an important research priority. International pregnancy registries are essential in developing better evidence-based practice guidelines, and neurologists should be encouraged to contribute to these when possible.
 - The management of women with multiple sclerosis, especially when they are taking disease-modifying agents, requires careful assessment of fertility and disease characteristics as well as a multidisciplinary approach to ensure positive outcomes in both mothers and their children.
-

Multiple sclerosis is a chronic inflammatory autoimmune disease characterised by inflammation and neurodegeneration.^{1,2} Around 75% of affected patients are women, with an average age of onset between 20 and 40 years.^{1,3} Although the exact incidence of women with multiple sclerosis who choose to become pregnant is not known, the impact of multiple sclerosis and its treatment on fertility, pregnancy and breastfeeding is a critical issue that needs to be managed in everyday clinical practice.^{4,5}

The aim of this review is to provide an overview of the unique family planning issues that affect people with multiple sclerosis, including the impact of multiple sclerosis and its treatment on fertility and planned and unplanned pregnancies, as well as a discussion of post partum care and breastfeeding. A review of the English literature published between 1995 and 2018 available on PubMed, Scopus and Google Scholar was conducted using the search terms “multiple sclerosis”, “MS”, “disease-modifying agents”, “teratogenicity”, “family planning”, “fertility”, “pregnancy” and “breastfeeding”.

Family planning considerations in patients with multiple sclerosis

The 1998 Pregnancy in Multiple Sclerosis (PRIMS) study was the first to demonstrate that the rate of relapse actually declined during pregnancy, especially in the third trimester (absolute relapse rate reduction, mean, 0.2; standard deviation [SD], 1.0) when compared with the year before pregnancy (absolute relapse rate reduction, mean, 0.7; SD, 0.9),⁶ with an increase relapse rate in the first 3 months post partum noted (mean, 1.2; SD, 2.0).⁶ This study led to a significant change in recommendations for women with multiple sclerosis, who were historically advised not to

conceive.⁷ In the current era of an increasing number of available disease-modifying treatments (DMTs), there is a growing need for clinicians to provide their patients with appropriate counselling on family planning.⁷ Unfortunately, there are only a few robust studies assessing the impact of multiple sclerosis therapy on pregnancy as a reference for physicians and their patients, and many of those studies available are limited by ethical concerns, real-world constraints and methodological issues.⁸ Even though data from larger observational registries are increasingly becoming available,^{9,10} these studies are still commonly hampered by small sample sizes that limit their ability to examine important outcomes such as specific birth defects or syndromes.⁸ While avoiding any potential drug exposure risks to the fetus seems prudent, discontinuation of treatment pre-conception is also associated with an increased risk of the reappearance of disease activity, especially if there are significant delays in conceiving.⁵

A treatment plan covering pre-pregnancy, pregnancy and the post partum period should therefore be developed in consultation with the patient for all women with multiple sclerosis who are planning a family. In addition, it may prove useful to consider these questions upfront in any woman who has been recently diagnosed with multiple sclerosis so that family planning and possible future pregnancies can be incorporated into discussions around choice of an initial DMT. Consideration should be given that most DMTs can have some delay in taking effect⁷ and starting a treatment that will be discontinued within a few months may have limited meaningful clinical effect. Conversely, a woman presenting with severe relapses or uncontrolled inflammatory activity may be best advised to delay pregnancy until disease control is optimised. A guidance for possible discussion points has been developed by the National Institute for Health and Care Excellence in the United Kingdom (Box 1).^{4,5,7,8}

Contraception in multiple sclerosis

As for all women of childbearing age, many women with multiple sclerosis may choose to delay pregnancy, choose not to have children, or consider their families complete. It is therefore important to be familiar with any potential for drug–drug interactions between contraceptive methods and DMTs or any other treatments. Fortunately, no known drug–drug interactions between currently available DMTs and contraceptives have been reported for therapies other than teriflunomide.¹⁰ Repeated doses of teriflunomide increase ethinylloestradiol and levonorgestrel peak serum concentrations and total drug exposure (area under the curve) in the body, but this is not expected to have an adverse impact on the efficacy of oral contraceptives.¹⁰ For those patients undergoing the accelerated elimination procedure for teriflunomide, both cholestyramine and activated charcoal may decrease the absorption of oestrogens and progestogens and, thus, the use of alternative contraceptive methods is recommended during this procedure.¹⁰

Impact of multiple sclerosis and disease-modifying treatments on fertility

Only a limited number of studies have assessed the impact of multiple sclerosis and its treatment on fertility.^{4,7,12} Results from a recent observational cohort study of 115 patients and 216 pregnancies (in 84 women) showed similar rates of spontaneous pregnancies per woman, time to pregnancy and spontaneous miscarriage rates compared with the general population.¹³ However, the mean number of children per woman with multiple sclerosis (1.37 children per woman) was lower than in the general population (1.99 children per woman).¹³ It is unclear whether this is due to decreased fertility as a result of the condition itself and its treatment, or if this finding merely reflects cautious attitudes towards pregnancy in women with multiple sclerosis.¹²

In addition to age-related reduction in ovarian reserve, several disease-related factors could potentially have a negative impact on fertility. These include issues relating to sexual dysfunction and, possibly, endocrine disturbances.^{12,14} Sexual dysfunction is common in multiple sclerosis, with a reported approximate prevalence of 40–80% in females, double that reported in the general population.¹⁵ An open discussion regarding lack of libido, vaginal dryness, anorgasmia, dysorgasmia and altered genital sensation may improve both the management and the patient's

quality of life.¹⁶ Furthermore, bladder dysfunction, fatigue and pain can also interfere with sexual health and require a comprehensive assessment and involvement of a rehabilitation physician or allied health professional. Iatrogenic causes of sexual dysfunction need to be minimised and can be observed in association with commonly used symptomatic therapies, including antidepressants and treatments for multiple sclerosis-related neuropathic pain, such as tricyclic antidepressants (eg, amitriptyline) and GABAergic agents (eg, gabapentin).¹⁷ Moreover, the potential teratogenicity of such symptomatic therapies need to be evaluated in a careful risk–benefit analysis.

Assisted reproduction in multiple sclerosis

Difficulties conceiving for patients with multiple sclerosis can lead to referral to fertility specialists.^{4,18} While there is no contraindication to undergo assisted reproductive therapy,¹⁸ treating physicians need to be aware that studies assessing the impact of assisted reproductive therapy on multiple sclerosis disease activity have consistently demonstrated an increased risk of relapse, potentially due to changing hormone levels, cessation of multiple sclerosis therapy and stress.¹⁸⁻²³ In particular, the use of pulses of gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (rather than GnRH antagonists) was found to increase multiple sclerosis relapse in the 3-month period following assisted reproductive therapy both in women who did and did not become pregnant.^{22,23} Ensuring disease stability before and during fertility treatment should be the goal.²⁴ This may include changing the patient's DMT during the conception period, which entails possible washout periods and additional monitoring that can add months to the patient's conception planning²⁵ (Box 2).

Counselling patients who experience an unplanned pregnancy

Experiencing an unplanned pregnancy can be an emotional time, particularly for people with a chronic illness such as multiple sclerosis.^{7,14} There may be concerns around the impact of the pregnancy on their health and that of their unborn child, genetic risks and concerns about parenting.^{7,14} Most women with multiple sclerosis experience normal pregnancies and the disease itself does not pose any specific risks to the fetus.²⁴ Indeed, a recent meta-analysis showed no significantly increased risk of obstetric and neonatal complications in women with multiple sclerosis.³⁴ Counselling regarding the risk of multiple sclerosis in offspring is important in order to allay unnecessary fears. Although there is no single gene that produces multiple sclerosis, familial multiple sclerosis does occur, with the frequency varying from 3% to 33% in some studies.³⁵ The lifetime risk of developing multiple sclerosis in children with a first degree relative with multiple sclerosis is increased six- to 12-fold from a baseline lifetime risk of 0.2% to 0.5%,¹⁴ suggesting that the likelihood of children of people with multiple sclerosis to develop the disease themselves remains very low.³⁶

Multiple sclerosis-associated neurological symptoms, particularly fatigue, present an additional burden both during pregnancy and post partum.^{4,7} In addition, concerns about parenting and child care in the case of possible multiple sclerosis disease progression may be exacerbated by the uncertainty about prognosis.^{4,7} Discussing community support services that are available in the local area may be useful, as well as connecting patients with other affected people through face-to-face or online support groups.

Women with multiple sclerosis who experience an unplanned pregnancy while taking DMTs will likely have concerns regarding possible teratogenic effects,¹⁴ particularly as retrospective audits suggest that up to 40% of pregnancies in patients with multiple sclerosis are exposed to 8 weeks of DMTs before cessation.³⁷ The timing of exposure to a potential teratogen — an agent that can cause functional or structural fetal developmental deficits mediated by causing cell death, altering tissue growth or cellular function — is critical, with the embryo (defined as the first 8 weeks post-conception) being most vulnerable.³⁹ During the second and third trimester, there is ongoing maturation and growth of limbs, organs, eyes, haematopoiesis, and the central nervous system,³⁹ and it cannot be

assumed that DMTs during this time would be safe. Apart from the late effects of natalizumab exposure (Box 2), the effects of other DMTs on fetal development during these stages of pregnancy are not known.

If exposure to DMTs with a less favourable pregnancy safety classification (Box 2) such as a Category D (eg, fingolimod or cladribine) or Category X drug occurred in the first trimester, the patient should be counselled, and comanagement with a high risk maternal fetal medicine clinic should be considered.⁷ This also applies to women who experience an unplanned pregnancy and wish to continue taking their DMT.³⁸ In the event of an unplanned pregnancy while taking teriflunomide, women are advised to undergo an accelerated elimination procedure until teriflunomide plasma concentrations fall below 0.02 mg/L to minimise risk to the fetus.³³ Some women (and couples) choose to terminate the pregnancy for a variety of reasons. There is no known increased risk associated with termination of pregnancy in its early stages in patients with multiple sclerosis in terms of relapse, anaesthesia or the procedure itself.^{40,41} Patients should be advised to cease DMTs on discovery of being pregnant and an appointment to discuss management should inform further decision making.

Management of patients who are planning a pregnancy

The risk of relapse in patients with multiple sclerosis decreases in pregnancy, particularly in the second and third trimesters.⁶ This reduction varies according to studies, but a recent meta-analysis of 23 studies on pregnancy in multiple sclerosis, reported an annualised relapse rate in the year before pregnancy as 0.44 per year, falling to 0.26 during pregnancy and increasing to 0.76 in the post partum period across the studies.³⁴ While the reasons for this variation in relapse rates have not been fully elucidated, it has been suggested that this may be a result of immunological changes, both in the innate and adaptive immune systems, that occur during pregnancy to protect the fetus from the mother's immune system.^{14,42}

The lack of long term and comprehensive studies has resulted in the universal recommendation that multiple sclerosis treatments are not safe for use in pregnancy and that, ideally, treatment should be discontinued before conception.⁴³ Elimination recommendations for the currently available therapies are based on their known pharmacokinetic profiles (Box 3).⁷ Contraception should be continued during the washout period to ensure that a pregnancy does not occur.^{4,43}

On the basis of currently available data, it appears that glatiramer acetate, dimethyl fumarate, alemtuzumab and daclizumab (globally withdrawn from the market in 2018 due to other safety concerns)⁴⁴ present the least risk of malformations or irreversible damage to the fetus in pregnancy, with all four being given a Category B pregnancy rating by the Australian Therapeutic Goods Administration (Box 2).¹⁰ In contrast, teriflunomide has been given a Category X pregnancy rating, as it has been shown to be teratogenic in rats and rabbits and may cause fetal harm in humans (Box 2).³³ Finally, cladribine, natalizumab, interferon- β , peginterferon- β -1a, fingolimod and ocrelizumab have been given Category C or Category D pregnancy ratings (Box 2).²⁶ It is important to note that drug classifications in pregnancy are based on the initial reproductive studies in animals and pre-registration clinical trials and are rarely updated as longer term data become available. For example, even though the large, global, observational Tysabri Pregnancy Exposure Registry showed that, in patients with multiple sclerosis ($n = 349$), natalizumab was associated with a spontaneous abortion rate consistent with that of the general population, it still maintains a Category C rating^{9,26} — Box 2 includes data on pregnancy and DMT exposures when available. Furthermore, the classification of drug safety in pregnancy can lead to confusion in that the alphabetical listing implies a definite hierarchical increase in fetal risk the further away from “A” the drug is listed.²⁶ For instance, Category C drugs could be suspected or shown to have caused harmful effects on the human fetus or neonate without causing malformations.²⁶ Such effects are often minor or reversible. For a drug to be classified as Category B, there had to have been at least limited exposure in pregnant women without malformations recorded.²⁶ Further subclassification is then dependent on the quality and outcomes of animal studies. This takes into consideration that, when no human data are available, a dose teratogenic in animals that is less than

tenfold higher than the maximum human therapeutic dose is suggestive of a high risk that the particular drug may be teratogenic in humans.³⁹

Understanding these classifications better may assist physicians in performing a more accurate risk–benefit assessment of the multiple sclerosis DMT-related risks, while recognising that the background population risk for any major malformation (without taking into account confounders such as maternal age) is 3–5%.³⁹

In recent years, the discussion regarding safety of treatment during pregnancy has become more nuanced with the recognition that decreasing the risk to the fetus by minimising drug exposure must be balanced against the risk of increased disease activity in the mother.⁴⁵ Cessation of multiple sclerosis DMTs can result in the reappearance of disease activity within weeks to months⁷ and can occasionally result in severe relapses, especially when withdrawing natalizumab and fingolimod.²⁸ Managing relapses in pregnancy with high dose corticosteroids in the first trimester is thought to be safe, despite occasional reports in animal studies of cleft palate and skeletal malformations.²⁷ While the decision to withdraw therapy may be relatively straightforward in patients with low levels of disease activity, for others with higher levels of disease activity or previous relapses during pregnancies, this can be more challenging.⁵ Ideally, the disease should be in remission and the patient should be switched to a drug with a better pregnancy safety classification (Box 2) before conception. Continuing DMT throughout the pregnancy is uncommon but has been reported using natalizumab^{30,46} and may be useful as a rescue therapy in patients with a known history of high pre-conception relapse rates that, in turn, can result in increased intrapartum and post partum relapse activity.²⁴ When using natalizumab in pregnancy, ceasing treatment at 29 weeks' gestation is often advised to minimise haematological abnormalities reported in newborns.³⁰

Family planning in males with multiple sclerosis

Recent evidence from Denmark has shown that men with male factor infertility have a higher risk of prevalent multiple sclerosis (odds ratio [OR], 1.6; 95% CI, 1.04–2.51), indicating a possible relationship between multiple sclerosis and male infertility.⁴⁷ As a result, it is important not to overlook counselling males with regards to possible fertility issues. There are currently no data that suggest any effect of DMTs on male fertility, and data on the impact of DMTs on birth outcomes in children fathered by men with multiple sclerosis are currently lacking.^{8,47} A small study assessing birth outcomes in 32 paternity cases of 46 children (30 under interferon- β , 12 under glatiramer acetate, two under natalizumab, one taking methotrexate, and one under azathioprine plus interferon- β -1b) suggested no negative impact on birth outcomes.⁴⁷ A recent retrospective analysis reported no structural defects or functional abnormalities in newborns with paternal teriflunomide exposure ($n = 22$), and there were no reports of embryofetal abnormalities in either of two induced abortions (Box 2).³³ While it is recommended that men with multiple sclerosis be informed of the limited available data, in practice, DMTs are rarely ceased in men with multiple sclerosis trying to conceive.

Post partum care and advice on breastfeeding

Management of women with multiple sclerosis during labour and delivery is generally left to the discretion of the obstetrician. Disease-related factors such as fatigue, lower limb weakness and spasticity need to be considered. In general, adequate anaesthesia to minimise fatigue should be a priority, and a birth plan should be discussed with the woman during prenatal care.³⁴

Discussions relating to post partum care should include a review of minimising the risk of post partum relapse, wishes around breastfeeding, and how this will affect re-initiation of DMTs.³⁸

Post partum relapse risk increases to about 32% higher than the pre-pregnancy relapse rate, peaking around 3 months after delivery.³⁴ Post partum relapses can be managed with high dose intravenous methylprednisolone, but the drug is excreted in breast milk and a feeding break of up to 8 hours after the dose is advisable.⁴⁸

Evidence regarding the optimal time to restart DMTs after pregnancy is currently lacking.⁴⁹ However, in general, for patients with active disease who required therapy before pregnancy, re-initiation should occur as early as possible after delivery once the patient ceases breastfeeding.⁵⁰ It is interesting that prospective data from a nationwide German registry suggested that exclusive breastfeeding for 6 months was modestly effective in reducing multiple sclerosis relapses,^{51,52} with data from a meta-analysis of 1558 patients suggesting a protective effect of breastfeeding independent of its duration (OR, 0.53; 95% CI, 0.34–0.82).⁵³ However, a definite recommendation cannot be made due to possible confounding factors in which the lower observed relapse rate may reflect mothers with stable pre-pregnancy disease choosing to breastfeed compared with those with active pre-pregnancy disease who restart DMTs.^{51,53} In practice, the choice to breastfeed should be discussed with the mother, taking into account their wishes, treatment options (Box 4) and pre-pregnancy disease activity.

No treatment for multiple sclerosis is currently listed as being safe for use while breastfeeding⁴³ (Box 4). The passage of molecules in breast milk is thought to be governed by the size of the molecules, with larger molecules (≥ 800 Da)⁵⁴ not being able to penetrate mammary epithelial cell junctions. Factors such as pKa (favouring weak bases) and protein binding may play a role, as might the presence of mastitis and the dosing schedule of the drug. Several agents are either not excreted in breast milk or are thought to be digested by the neonatal gastrointestinal tract, which becomes impermeable to large molecules after the first few days of life (Box 4).⁴³ Breastfeeding while exposed to monoclonal antibodies (molecular weight $\sim 140\,000$ kDa) used in inflammatory bowel disease⁵⁵ and rheumatoid arthritis⁵⁶ has been studied more thoroughly than in multiple sclerosis. It appears that monoclonal antibodies concentrations in breast milk rise to a peak concentration within a few hours.⁵⁴ However, cases in which drug levels were measured sequentially have shown an ongoing increase in drug concentration in milk for several days after a dose — the maximum concentration was reached on Day 50 with a surprisingly high relative infant dose of 5.3%.⁵⁷ Despite the concentrations of most monoclonal antibodies found in breast milk being low, much is still unknown about the long term effect of even small concentrations of biological drugs on the developing immune system of infants.

Conclusion

As a result of their widespread use, elucidating the influence of DMTs on fertility, pregnancy and breastfeeding is critical for assisting physicians and patients in weighing up the relative risks and benefits of continuing therapy. International pregnancy registries have a key role to play, and neurologists should be encouraged to contribute to these when possible. Furthermore, family planning counselling may be useful for patients with multiple sclerosis to help alleviate fears and concerns and to enable more informed decision making. A multidisciplinary approach, involving collaboration between neurologists, obstetricians, midwives, anaesthesiologists and fertility specialists (when required), is also recommended to help optimise outcomes for both the patient and the child. Decision making should be a shared experience between patient and physician, with a personalised approach developed to meet the unique needs of each individual patient.

Competing interests: Anneke Van der Walt has received travel support, speaking honoraria and served on advisory boards for Biogen Australia, Novartis, Merck, Sanofi, Roche and Teva. Ai-Lan Nguyen has received grant support and travel support from Biogen Australia. Vilija Jokubaitis has received travel support and speaking honoraria from Biogen Australia.

Provenance: Not commissioned; externally peer reviewed.

Author details

Anneke Van Der Walt^{1,2,3,4}

Ai-Lan Nguyen^{2,4}

Vilija Jokubaitis^{1,2,3}

1 Monash University, Melbourne, VIC.
2 University of Melbourne, Melbourne, VIC.
3 Alfred Health, Melbourne, VIC.
4 Royal Melbourne Hospital, Melbourne, VIC.
Anneke.VanDerWalt@monash.edu
doi: 10.5694/mja18.00055

References

- 1 Niedziela N, Adamczyk-Sowa M, Pierzchała K. Epidemiology and clinical record of multiple sclerosis in selected countries: a systematic review. *Int J Neurosci* 2014; 124: 322-330.
- 2 Hauser S, Oksenberg J. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. *Neuron* 2006; 52: 61-76.
- 3 Australian Bureau of Statistics. Multiple sclerosis (Cat. No. 4429.0). Canberra: Commonwealth of Australia, 2012. <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4429.0main+features100182009> (viewed Dec 2017).
- 4 Amato MP, Portaccio E. Fertility, pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs* 2015; 29: 207-220.
- 5 Broadley SA, Barnett MH, Boggild M, et al. A new era in the treatment of multiple sclerosis. *Med J Aust* 2015; 203: 139-141. <https://www.mja.com.au/journal/2015/203/3/new-era-treatment-multiple-sclerosis>
- 6 Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. *N Engl J Med* 1998; 339: 285-291.
- 7 Vukusic S, Marignier R. Multiple sclerosis and pregnancy in the "treatment era". *Nat Rev Neurol* 2015; 11: 280-289.
- 8 Lu E, Wang BW, Alwan S, et al. A review of safety-related pregnancy data surrounding the oral disease-modifying drugs for multiple sclerosis. *CNS Drugs* 2014; 28: 89-94.
- 9 Friend S, Richman S, Bloomgren G, et al. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) Pregnancy Exposure Registry: a global, observational, follow-up study. *BMC Neurol* 2016; 16: 150.
- 10 Therapeutics and Goods Administration. TGA eBusiness Services. Australian Government Department of Health and Ageing. <https://www.tga.gov.au/prescribing-medicines-pregnancy-database> (viewed Dec 2017).
- 11 National Clinical Guideline Centre (UK). Multiple sclerosis: management of multiple sclerosis in primary and secondary care (NICE clinical guidelines no. 186). London: National Institute for Health and Care Excellence (UK), 2014. <https://www.ncbi.nlm.nih.gov/books/NBK248064> (viewed Dec 2017).
- 12 Cavalla P, Rovei V, Masera S, et al. Fertility in patients with multiple sclerosis: current knowledge and future perspectives. *Neurol Sci* 2006; 27: 231-239.
- 13 Roux T, Courtillot C, Debs R, et al. Fecundity in women with multiple sclerosis: an observational mono-centric study. *J Neurol* 2015; 262: 957-960.
- 14 Borisov N, Döring A, Pfueller CF, et al. Expert recommendations to personalization of medical approaches in treatment of multiple sclerosis: an overview of family planning and pregnancy. *EPMA J*; 2012; 3: 9.
- 15 Cordeau D, Courtois F. Sexual disorders in women with MS: assessment and management. *Ann Phys Rehabil Med* 2014; 57: 337-347.
- 16 Schärer LC, Foley FW, Zemon V, et al. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. *Mult Scler* 2014; 20: 610-616.
- 17 Multiple Sclerosis International Foundation. Intimacy and sexuality. *MS in focus* 2005; 6. <https://www.msif.org/wp-content/uploads/2014/09/MS-in-focus-6-Intimacy-and-sexuality-English.pdf> (viewed Dec 2017).
- 18 Hellwig K, Correale J. Artificial reproductive techniques in multiple sclerosis. *Clin Immunol* 2013; 149: 219-224.
- 19 Laplaud DA, Leray E, Barrière P, et al. Increase in multiple sclerosis relapse rate following in vitro fertilization. *Neurology* 2006; 66: 1280-1281.
- 20 Hellwig K, Schmirigk S, Beste C, et al. Increase in relapse rate during assisted reproduction technique in patients with multiple sclerosis. *Eur Neurol* 2009; 61: 65-68.
- 21 Hellwig K, Beste C, Brune N, et al. Increased MS relapse rate during assisted reproduction technique. *J Neurol* 2008; 255: 592-593.
- 22 Michel L, Foucher Y, Vukusic S, et al. Increased risk of multiple sclerosis relapse after in vitro fertilisation. *J Neurol Neurosurg Psychiatr* 2012; 83: 796-802.
- 23 Correale J, Farez MF, Ysraelit MC. Increase in multiple sclerosis activity after assisted reproduction technology. *Ann Neurol* 2012; 72: 682-694.
- 24 Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mult Scler* 2014; 20: 739-746.
- 25 Coyle PK. Switching therapies in multiple sclerosis. *CNS Drugs* 2013; 27: 239-247.
- 26 Australian categorisation system for prescribing medicines in pregnancy. Therapeutic Goods Administration, 2011. www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy (viewed Dec 2017).
- 27 Gur C, Diav-Citrin O, Shechtman S, et al. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004; 18: 93-101.
- 28 Coyle PK. Multiple sclerosis and pregnancy prescriptions. *Expert Opin Drug Saf* 2014; 13: 1565-1568.
- 29 Achiron A, Chambers C, Fox EJ, et al. Pregnancy outcomes in patients with active RRMS who received alemtuzumab in the clinical development program. *Mult Scler J* 2015; 21: 581-582; P1120.
- 30 Haghighi A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. *JAMA Neurol* 2014; 71: 891-895.
- 31 Vukusic S, Kappos L, Wray S, et al. An update on pregnancy outcomes following ocrelizumab treatment in patients with multiple sclerosis and other

- autoimmune diseases. *Mult Scler J* 2017; 23: 85-426; P710.
- 32 Glazaka A, Nolting A, Cook S, et al. Pregnancy outcomes during the clinical development programme of cladribine in multiple sclerosis (MS): an integrated analysis of safety for all exposed patients. *Mult Scler J* 2017; 23: 976-1023; P1874.
- 33 Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. *Neurol Ther* 2014; 3: 133-138.
- 34 Finkelsztejn A, Brooks J, Paschoal FM, Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. *BJOG* 2011; 118: 790-797.
- 35 Harirchian MH, Fatehi F, Sarraf P, et al. Worldwide prevalence of familial multiple sclerosis: a systematic review and meta-analysis. *Mult Scler Relat Disord* 2018; 20: 43-47.
- 36 Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; 372: 1502-1517.
- 37 Fragoso YD, Boggild M, Macias-Islas MA, et al. The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis. *Clin Neurol Neurosurg* 2013; 115: 154-159.
- 38 Houtchens MK, Kolb CM. Multiple sclerosis and pregnancy: therapeutic considerations. *J Neurol* 2013; 260: 1202-1214.
- 39 Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. *CMAJ* 2002; 167: 265-273.
- 40 Alwan S, Yee IM, Dybalski M, Guimond C, Dwosh E, Greenwood TM, et al. Reproductive decision making after the diagnosis of multiple sclerosis (MS). *Mult Scler* 2013; 19: 351-358.
- 41 Ferrero S, Pretta S, Ragni N. Multiple sclerosis: management issues during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2004; 115: 3-9.
- 42 Iorio R, Frisullo G, Nociti V, et al. T-bet, pSTAT1 and pSTAT3 expression in peripheral blood mononuclear cells during pregnancy correlates with post-partum activation of multiple sclerosis. *Clin Immunol* 2009; 131: 70-83.
- 43 Broadley SA, Barnett MH, Boggild M, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 3, treatment practicalities and recommendations. *J Clin Neurosci* 2014; 21: 1857-1865.
- 44 Daclizumab withdrawn from the market worldwide [erratum for Daclizumab for MS]. *Drug Ther Bull* 2018; 56: 38-21.
- 45 Broadley SA, Barnett MH, Boggild M, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 1, historical and established therapies. *J Clin Neurosci* 2014; 21: 1835-1846.
- 46 Hellwig K, Haghikia A, Gold R. Pregnancy and natalizumab: results of an observational study in 35 accidental pregnancies during natalizumab treatment. *Mult Scler* 2011; 17: 958-963.
- 47 Glazer CH, Tøttenborg SS, Giwercman A, et al. Male factor infertility and risk of multiple sclerosis: a register-based cohort study. *Mult Scler* 2017; 46: 1-8.
- 48 Strijbos E, Coenradie S, Touw DJ, Aerden L. High-dose methylprednisolone for multiple sclerosis during lactation: concentrations in breast milk. *Mult Scler* 2015; 21: 797-798.
- 49 Hellwig K, Haghikia A, Gold R. Parenthood and immunomodulation in patients with multiple sclerosis. *J Neurol* 2010; 257: 580-583.
- 50 Vukusic S, Durand-Dubief F, Benoit A, et al. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. *Mult Scler* 2015; 21: 953-955.
- 51 Hellwig K, Rockhoff M, Herbstritt S, et al. Exclusive breastfeeding and the effect on postpartum multiple sclerosis relapses. *JAMA Neurol* 2015; 72: 1132-1138.
- 52 Conradi S, Malzahn U, Paul F, et al. Breastfeeding is associated with lower risk for multiple sclerosis. *Mult Scler* 2013; 19: 553-558.
- 53 Pakpoor J, Disanto G, Lacey MV, et al. Breastfeeding and multiple sclerosis relapses: a meta-analysis. *J Neurol* 2012; 259: 2246-2248.
- 54 Anderson PO. Monoclonal antibodies. *Breastfeed Med* 2016; 11: 100-101.
- 55 McConnell RA, Mahadevan U. Pregnancy and the patient with inflammatory bowel disease: fertility, treatment, delivery, and complications. *Gastroenterol Clin North Am* 2016; 45: 285-301.
- 56 Levy RA, de Jesús GR, de Jesús NR, Klumb EM. Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation. *Autoimmun Rev* 2016; 15: 955-963.
- 57 Baker TE, Cooper SD, Kessler L, Hale TW. Transfer of natalizumab into breast milk in a mother with multiple sclerosis. *J Hum Lact* 2015; 31: 233-236.

[Insert boxes]

[Box 1]

1 Recommendation* for counselling patients of childbearing age diagnosed with multiple sclerosis¹¹

Explain to women of childbearing age with multiple sclerosis that:

- relapse rates may reduce during pregnancy and may increase 3–6 months after childbirth;
- pregnancy does not increase the risk of progression of disease

If a person with multiple sclerosis is thinking about pregnancy, give them an opportunity to discuss with an appropriate health care professional issues such as:

- fertility;
- in vitro fertilisation;
- the risk of the child developing multiple sclerosis;
- use of vitamin D before conception and during pregnancy;
- medication use in pregnancy;
- pain relief during delivery (including epidurals);
- care of the child;
- breastfeeding

* Adapted from the clinical guidelines from the National Institute for Health and Care Excellence, developed based on a graded systematic review of the literature.¹¹

[Box 2]

2 Summary of fertility, pregnancy and lactation risks of disease-modifying treatments currently approved for the management of multiple sclerosis in Australia^{10,26}

	Fertility	Pregnancy	
		Licensed classification ¹⁰	Post-marketing data
High dose IV methylpred-nisolone	None known	Category A: safe in pregnancy	Cases of cleft palate and skeletal malformations in animals reported ²⁷
Glatiramer acetate	No adverse effects observed in animal studies	Category B1: limited information in humans; no adverse effects on embryofetal development observed in animal studies	Analysis of 246 pregnancies in the German, Italian and other multiple sclerosis and pregnancy registries have found no evidence of abortion, adverse fetal outcomes or other evidence of harm ²⁸
Dimethyl fumarate	No adverse effects observed in animal studies	Category B1: limited information in humans; not teratogenic, but adverse effects on embryofetal development and abortifacient activity observed at high doses in animal studies	39 pregnancies with known outcomes: ²⁸ <ul style="list-style-type: none"> ▪ 26 live births; ▪ 3 spontaneous abortions; ▪ 10 elective terminations
Alemtuzumab	Azoospermia and reduction in corpora lutea and implantation sites observed in animal studies	Category B3: limited information in humans; abortifacient activity observed in animal studies	Data on 183 out of 193 exposed pregnancies: ²⁹ <ul style="list-style-type: none"> ▪ 122 live births (1 case of thyrotoxic crisis in neonate); ▪ 39 spontaneous abortions; ▪ 19 elective abortions; ▪ 1 stillbirth (4 years after last dose)
Natalizumab	Reduced female fertility observed in animal studies at high doses; no effects on male fertility in animal studies at high doses	Category C: limited information in humans; abortifacient but not teratogenic activity observed in animal studies	101 exposed pregnancies, compared with matched controls: ⁸ <ul style="list-style-type: none"> ▪ no risk of malformations, low birthweight or premature birth <p>A series of 13 pregnancies with natalizumab throughout:³⁰</p> <ul style="list-style-type: none"> ▪ 10/13 neonates had mild, self-resolving haematologic changes
Ocrelizumab	No effects observed in animal studies at high doses	Category C: no adequate data in humans; no evidence of maternal toxicity, teratogenicity or embryotoxicity in animal studies, but impacts on pre- and postnatal development were observed	From clinical trials in multiple sclerosis, 25 exposed pregnancies (the last infusion occurred within 3 months of conception, during pregnancy or if the date was unknown): ³¹ <ul style="list-style-type: none"> ▪ 11 full-term births; ▪ 2 pre-term births; ▪ 7 elective terminations (no abnormalities in products of

			conception); <ul style="list-style-type: none"> ▪ 1 stillbirth; ▪ 4 ongoing pregnancies
Cladribine	Reduced testicular and epididymal weights, sperm motility and sperm counts observed in animal studies	Category D: limited information in humans; abortifacient and teratogenic activity observed in animal studies	From clinical trials in multiple sclerosis; 17 pregnancies documented: ³² <ul style="list-style-type: none"> ▪ 10 terminations; ▪ 4 spontaneous abortions; ▪ 1 abortion not specified; ▪ 2 healthy infants
Fingolimod	No adverse effects observed in animal studies	Category D: limited information in humans; abortifacient activity observed in animal studies	89 pregnancies on fingolimod (61 first trimester exposures): ⁸ <ul style="list-style-type: none"> ▪ 2 births with fetal malformations; ▪ 4 terminations due to fetal malformations; ▪ 9 spontaneous abortions; ▪ 20 elective terminations
Interferon- β -1a (SC)	No adverse effects observed in animal studies	Category D: abortifacient activity observed in animal studies with other interferons; not teratogenic in animal studies	German Multiple Sclerosis Pregnancy Registry; 251 pregnancies exposed to interferon- β -1a compared with 194 unexposed pregnancies. ²⁸ No differences between groups regarding: <ul style="list-style-type: none"> ▪ mean birthweight or length; ▪ pre-term birth; ▪ spontaneous abortion; ▪ congenital anomalies
Interferon- β -1a (IM)	Menstrual cycle irregularities and associated progesterone concentration changes observed in animal studies	Category D: limited information in humans; abortifacient activity observed in animal studies; not teratogenic in animal studies; limited information in humans	
Interferon- β -1b (SC)	No effects on menstrual cycle or hormone profiles in animal studies	Category D: limited information in humans; abortifacient but not teratogenic activity observed in animal studies	
Peginterferon- β -1a (SC)	Menstrual irregularities, anovulation and decreased serum progesterone in animal studies	Category D: limited information in humans; not teratogenic but abortifacient activity observed at high doses in animal studies	
Teriflunomide	No adverse effects observed in animal studies	Category X: limited information in humans; may cause fetal harm. Teratogenicity and embryo lethality	70 exposed pregnancies and 22 pregnancies in female partners of men receiving teriflunomide: ³³

- noted in offspring of rats and rabbits.
- 42 live births;
 - 31 Induced abortions;
 - 14 spontaneous abortions;
 - 2 unknown/ongoing

IM = intramuscular. IV = intravenous. SC = subcutaneous. **Category B.** Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. **Category B1.** Studies in animals have not shown evidence of an increased occurrence of fetal damage. **Category B2.** Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. **Category B3.** Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.²⁶ **Category C.** Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.²⁶ **Category D.** Drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.²⁶ **Category X.** Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.²⁶

[Box 3]

3 Summary of recommended discontinuation periods before conception based on elimination half-life of disease-modifying drugs currently approved for the treatment of multiple sclerosis in Australia¹⁰

	Elimination half-life	Recommended minimal discontinuation period before conception
Alemtuzumab (mean)	2 days	4 months
Cladribine (mean)	5.4 hours	6 months
Dimethyl fumarate (mean)	1 hour	1 month*
Fingolimod, (mean)	6–9 days	2 months
Glatiramer acetate (mean)	20 hours	1 month
Interferon- β -1a (SC) (median)	66 hours	1 month
Interferon- β -1a (IM) (mean)	10 hours	1 month
Interferon- β -1b (SC) (mean)	4.3 hours	1 month
Natalizumab, mean (SD)	11 days (4 days)	2–3 months
Ocrelizumab (mean)	26 days	6 months
Peginterferon- β -1a (SC), mean (SE)	78 hours (15 hours)	1 month*
Teriflunomide (median)	19 days	~3.5 months
An 11-day accelerated elimination procedure, with cholestyramine or activated charcoal, can be used [†]		

IM = intramuscular. SC = subcutaneous. SD = standard deviation. SE = standard error. * Based on half-life alone. No formal recommendations are provided in the approved product information. † Both cholestyramine and activated charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure. Thus, alternative contraceptive methods are recommended.¹⁰

[Box 4]

4 Safety of multiple sclerosis disease-modifying treatments during lactation^{7,10,43}

Disease-modifying treatments	Excretion into milk and recommendations
Alemtuzumab	Excretion in milk observed in animal studies. Breastfeeding should be discontinued during treatment and for at least 4 months after treatment
Cladribine	It is not known whether cladribine is excreted in human milk. Women should not breastfeed during treatment or for 4 months after receiving cladribine
Dimethyl fumarate	It is not known whether dimethyl fumarate is excreted in animal or human milk. Breastfeeding is not recommended
Fingolimod	Fingolimod is excreted in the milk of treated animals during lactation at concentrations two- to threefold higher than that found in maternal plasma; owing to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving fingolimod should not breastfeed
Glatiramer acetate	It is not known whether glatiramer acetate or its metabolites are excreted in animal or human milk. Caution is advised
Interferon- β (β -1a and β -1b)	Low levels detected in breast milk. Risks versus benefits need to be carefully considered before breastfeeding on treatment
Natalizumab	Natalizumab has been detected in human milk; reduced offspring viability observed in animal studies at high maternal doses. Breastfeeding should be discontinued during treatment
Ocrelizumab	It is not known whether ocrelizumab is excreted in human milk. Breastfeeding should be discontinued during treatment and for 6 months after receiving ocrelizumab
Teriflunomide	Excretion in milk observed in animal studies. Breastfeeding is contraindicated
High dose intravenous methylprednisolone ⁴⁸	Excretion in breast milk in humans with peak concentrations at 2 hours after dose. Interrupting breastfeeding for 4–8 hours after a 1 g dose recommended

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Van Der Walt, A;Ai-Lan, N;Jokubaitis, V

Title:

Family planning, antenatal and post partum care in multiple sclerosis: a review and update

Date:

2019-09-01

Citation:

Van Der Walt, A., Ai-Lan, N. & Jokubaitis, V. (2019). Family planning, antenatal and post partum care in multiple sclerosis: a review and update. MEDICAL JOURNAL OF AUSTRALIA, 211 (5), pp.230-236. <https://doi.org/10.5694/mja2.50113>.

Persistent Link:

<http://hdl.handle.net/11343/285646>