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REVIEW

Disease-Modifying Drugs and Family Planning in People with Multiple Sclerosis: A Consensus Narrative Review from the Gulf Region

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ABSTRACT

Most disease-modifying drugs (DMDs) are contraindicated in pregnancy. Management of MS is especially challenging for pregnant patients, as withdrawal of DMDs leave the patient at risk of increased disease activity. We, a group of experts in MS care from countries in the Arab Gulf, present our consensus recommendations on the management of MS in these patients. Where possible, a patient planning pregnancy can be switched to a DMD considered safe in this setting. Interferon β now can be used during pregnancy, where there is a clinical need to maintain treatment, in addition to glatiramer acetate. Natalizumab (usually to 30 weeks' gestation for patients with high disease activity at high risk of relapse and disability progression) may also be continued into pregnancy. Cladribine tablets and alemtuzumab have been hypothesised to act as immune reconstitution therapies (IRTs). These drugs provide a period of prolonged freedom from relapses for many patients, but the patient must be prepared to wait for up to 20 months from initiation of therapy before becoming pregnant. If a patient

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becomes pregnant while taking fingolimod, and requires continued DMD treatment, a switch to interferon β or natalizumab after a variable washout period may be prescribed, depending on the level of disease activity. Women who wish to breastfeed should be encouraged to do so, and interferon β may also be used during breastfeeding. There is a lack of data regarding the safety of using other DMDs during breastfeeding.

Keywords: Breastfeeding; Disease-modifying drugs; Family planning; Multiple sclerosis; Pregnancy

Key Summary Points

The management of MS is especially challenging for pregnant patients, as most disease-modifying drugs (DMDs) are contraindicated at this time

We, a group of experts in MS care from countries in the Arab Gulf, present our consensus recommendations on the management of MS in these patients

Interferon β now can be used during pregnancy and breastfeeding, where there is a clinical need to maintain treatment, in addition to glatiramer acetate

Natalizumab (usually to 30 weeks' gestation for patients with high disease activity at high risk of relapse and disability progression) may also be continued into pregnancy

Pharmacological immune reconstitution therapies (currently cladribine tablets and alemtuzumab) provide prolonged freedom from relapses for many patients, but pregnancy should not occur for up to 20 months from initiation of therapy

Consider a switch to interferon β or natalizumab after an appropriate washout period for women who become pregnant on fingolimod

INTRODUCTION

Multiple sclerosis (MS) is diagnosed around 30 years of age, on average, a figure which has tended to decrease over time [1, 2]. A diagnosis of MS therefore commonly arises during women's childbearing years. Indeed, MS affects about 2–3 times as many women as men during these years of life [1]. The majority of people who develop MS are women, and a marked increase in the prevalence of MS in most countries has further increased the number of women who develop MS at a time that they are likely to consider planning a family [2–4].

These trends in the epidemiology of MS are evident in the authors' countries in the Gulf region, as elsewhere [5–7]. Large families are the norm in the Middle East, and cultural issues relating to contraception (and termination of a pregnancy exposed to a potentially unsafe therapy) must be discussed carefully [8, 9]. MS has no adverse impact per se on a woman's fertility, or on a pregnancy; conversely, pregnancy has no long-term impact on the course of MS (aside from short-term changes in relapse rates during and after a pregnancy, which are discussed in more detail below) [10]. Nevertheless, the onset of MS can have a profound influence on patients' reproductive choices: studies have shown that the fear and uncertainty provoked by the diagnosis resulted in these women having fewer pregnancies than they expected to have, had they not developed MS [11, 12]. Pregnancy also impacts on the management of MS. For example, women with MS commonly stop taking their disease-modifying drug (DMD) treatment for this reason because of concerns relating to the potential for adverse effects of the treatment on the pregnancy [13, 14]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

METHODS AND OBJECTIVES

An expert group in the UK has provided guidance on the management of people with MS who are planning a family [15], but otherwise

guidance is limited. Prescribing practices in Gulf countries are influenced by international labelling, e.g. from the European medicines Agency or the US Food and Drug Administration, but are not constrained by them [16]. Accordingly, international guidelines for the management of MS may not fully support local practice in the Gulf region. This article provides consensus recommendations on the application of DMD-based therapy for MS during pregnancy from a group of specialists in the management of MS in countries in the Arabian Gulf, considering in particular the impact of low or high levels of MS disease activity on management. Efficacy and the safety/tolerability and monitoring burdens of individual DMDs are key aspects to consider when prescribing a DMD, irrespective of pregnancy status or plans. A full account of these is beyond the scope of this review and has been reviewed elsewhere [17–19].

The expert consensus described in this article arose from a closed meeting (in Muscat, Oman, November 2019) in which all authors participated; delegates from Kuwait, Oman, Qatar, and the United Arab Emirates participated. The expert consensus is supported by a narrative review, based on presentations at this meeting, supplemented by additional literature searches and material provided by co-authors. The level of consensus on recommendations within the expert group was explored by open voting: a "high" level of consensus was defined arbitrarily as supported by at least 7–8/9 experts, moderate consensus was defined as being supported by 4–6/9 experts, and lower support was defined as a "low" level of consensus.

PRINCIPLES OF MANAGEMENT OF MS BEFORE, DURING, AND AFTER PREGNANCY

Preconception Counselling

Misconceptions relating to the practicability of completing a pregnancy are common among patients with MS [1–12], and patients should be counselled carefully that their MS has no impact on their ability to conceive, to carry the pregnancy to term, and to give birth to a healthy neonate [20]. In the authors' experience, patients are often concerned that they will pass on their MS to the children. Although there is familial clustering in MS, this is not considered to be a hereditary disease per se, as the overall risk of developing MS depends on interactions between genetic and environmental factors [21]. Patients may be counselled that the risk of MS in their children is low.

Need for Active Treatment of MS During Pregnancy?

On average, the frequency of relapses in a woman with MS declines during pregnancy, especially during the second and third trimesters, but then increases markedly during the 3 months following delivery [22, 23]. These observations and concerns regarding possible adverse effects to the foetus have led most women to discontinue DMD therapy during pregnancy. This position is reinforced by current (2018) European guidelines for the management of MS [24, 25] and an expert position statement from Italy [26], which have supported continued use of certain DMDs (interferon, glatiramer acetate, natalizumab) into pregnancy, within a multidisciplinary approach, especially for women with persistent high disease activity or who are at high risk of disease reactivation. US guidelines (also 2018) recommend that women may defer use of DMDs until after their pregnancy [19, 25]. A study from two pregnancy registries in the Middle East found a higher rate of relapses than reported previously in a population of women with MS who had mostly received "platform" or "first-line" therapies in the year before conception, such as glatiramer acetate or interferon, perhaps indicating a greater need for continued treatment at this time that was considered previously [27]. Importantly, we have little information on the rate of relapses during pregnancy in women with higher pre-conception levels of MS disease activity.

Thus, the choice of DMD for a female patient of childbearing potential will be influenced by her plans for starting a family, as becoming

pregnant may provoke an immediate change in treatment. Decisions on maintaining or switching treatment are complex and will be influenced by the patient's individual circumstances. Important considerations at this time include the risks to the foetus of the patient's current DMD, the level of disease activity experienced by the patient, the required washout period for the current DMD, and the time needed for the new DMD's efficacy to build up.

Research into the use of DMDs by women who are either pregnant or planning to become pregnant has continued, with a particular focus on gathering outcomes from registries dedicated to this purpose (see below), and statements such as "DMDs are not licensed during pregnancy, except glatiramer acetate" from the European MS guidelines are no longer clearly consistent with prescribing recommendations (Table 1). Indeed, the support for use of individual DMDs during pregnancy within their labelling varies widely between individual agents (Table 1). Teriflunomide, cladribine tablets, fingolimod, and siponimod have absolute contraindications for use during pregnancy in both the USA and Europe. Glatiramer acetate may be continued into pregnancy according to both US and European labels, as long as this is supported by an assessment of risks to the foetus and benefits to the mother. Dimethyl fumarate, alemtuzumab, natalizumab, and ocrelizumab may be used in Europe, according to such a risk:benefit assessment, but their use in pregnancy is discouraged (with warnings of potential "foetal harm"; thier use is contraindicated in the USA. The use of all preparations of interferon β in pregnancy is more strongly supported in Europe.

Current Data on DMDs and Pregnancy

Nature of the Evidence Base

The current evidence base from clinical studies regarding the use of individual DMDs in pregnancy is summarised below. For convenience we have divided the DMDs arbitrarily into the commonly used categories of "first-line" or "platform" DMDs (which usually include dimethyl fumarate, glatiramer acetate, interferon β, and teriflunomide) and "high-efficacy" DMDs (alemtuzumab, cladribine tablets, fingolimod, natalizumab, ocrelizumab) [17]. We have sought to cite papers from peer-reviewed journals here. However, the application of DMD-based therapy in the setting of pregnancy is an evolving science and many of the reports considered below are recent presentations at major congresses. These are included to provide the best snapshot possible of the current state of the science.

Platform DMDs

Glatiramer acetate This treatment has no teratogenic effects, according to data from national registries. In the Italian Multiple Sclerosis Register, analysis of data from 427 pregnancies in mothers with MS from 21 centres found no additional risk of spontaneous abortion or other adverse maternal or foetal outcomes [28, 29]. A total of 151 women with MS in Germany had been taking glatiramer acetate before the pregnancy, of whom 148 discontinued treatment in the first trimester and 3 discontinued treatment in the second trimester; 95 pregnancies unexposed to DMDs served as a control group [30]. There was no difference between groups for the proportions of live births or the risk of spontaneous abortion, any congenital anomaly, major congenital anomaly, preterm birth or need for caesarean section. In another study, evaluation of 5042 pregnancies exposed to glatiramer acetate demonstrated low and comparable rates of adverse pregnancy outcomes compared with data from two control databases of birth outcomes that together include > 1.7 million births each year [31]. Glatiramer acetate therefore appears to be safe with regard to use in pregnancy, at least during the first trimester.

Dimethyl fumarate Analysis of 63 pregnancies in women enrolled in clinical trials and of 135 pregnancies arising from post-marketing reports revealed no adverse effects on pregnancy outcomes [32]. An international registry is tracking pregnancies in women exposed to dimethyl fumarate; a recent report from this database (194 pregnancies with known outcome) showed that the rate of premature loss of the foetus was 9%, with live births occurring in the remainder, and a rate of birth defects of 4% [33]. To date,

Table 1 Current restrictions on the use of disease-modifying drugs (DMDs) relevant to pregnancy and breastfeeding

	Europe (European Medicines Agency)	USA (Food and Drug Administration
Platform/first-line DMDs		
Dimethyl fumarate	**Pregnancy**: Not recommended during pregnancy and in women of childbearing potential not using contraception; use in pregnancy only if clearly needed and if potential benefit justifies potential risk to foetus **Breastfeeding**: Decide on the balance of benefit of breastfeeding to infant with benefit of therapy to the mother	**Pregnancy**: "Based on animal data, may cause fetal harm", **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Glatiramer acetate (GA)	**Pregnancy**: Preferable to avoid use of GA during pregnancy unless benefit to mother outweighs the risk to foetus **Breastfeeding**: Decide on the balance of benefit of breastfeeding to infant with benefit of therapy to the mother	**Pregnancy**: Insufficient human data to evaluate risk to foetus **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Interferon β[a]	**Pregnancy**: Consider use considered during pregnancy if clinically needed (based on >1,000 pregnancy outcomes) **Breastfeeding**: No harmful effects on breastfed infant are anticipated; can be used during breast-feeding	**Pregnancy**: Use if benefits to the mother outweigh risks to the foetus **Breastfeeding**: it is not known whether interferonβ is present in breast milk[b]; Administer with caution to a nursing mother[c]
Teriflunomide	**Pregnancy**: Contraindicated **Breastfeeding**: Contraindicated	**Pregnancy**: Contraindicated: use accelerated drug elimination procedure if pregnancy occurs on treatment **Breastfeeding**: Women should not breastfeed during treatment
High-efficacy DMDs		
Alemtuzumab	**Pregnancy**: Maintain contraception for 4 months after the last dose. Use in pregnancy only if the potential benefit justifies the potential risk to the foetus. **Breastfeeding**: Avoid breastfeeding during and for 4 months after each treatment course (but balance potential benefit of breastfeeding with potential risks from exposure to drug)	**Pregnancy**: may cause foetal harm; maintain contraception for at least 4 months after the last dose **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Cladribine tablets	**Pregnancy**: Contraindicated – women should not become pregnant for at least 6 months after the last dose **Breastfeeding**: Contraindicated – women should not breastfeed for at least 1 week after the last dose	**Pregnancy**: Contraindicated – women should not become pregnant for at least 6 months after the last dose **Breastfeeding**: Contraindicated– women should not breastfeed for at least 10 days after the last dose
Fingolimod	**Pregnancy**: Contraindicated **Breastfeeding**: Contraindicated	**Pregnancy**: Contraindicated; women should not become pregnant for at least 2 months after stopping treatment **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Natalizumab	**Pregnancy**: Consider discontinuing treatment if a woman becomes pregnant during treatment; if treatment is continued, monitor newborn for haematological abnormalities **Breastfeeding**: Contraindicated – breast-feeding should be discontinued during treatment	**Pregnancy**: "Based on animal data, may cause fetal harm", **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Ocrelizumab	**Pregnancy**: Avoid during pregnancy unless potential benefit to the mother outweighs the potential risk to the foetus **Breastfeeding**: Advise women to discontinue breast-feeding during treatment	**Pregnancy**: Women of childbearing potential should use contraception during and for 6 months after treatment **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother
Siponimod	**Pregnancy**: Contraindicated **Breastfeeding**: Contraindicated	**Pregnancy**: Contraindicated; women should not become pregnant for at least 10 days after stopping treatment **Breastfeeding**: Consider benefits of breastfeeding against possible risks to the foetus and the clinical need of the mother

Abstracted from European Summaries of Product Characteristics and US Prescribing Information. Colours are applied arbitrarily according to strength of support for use during pregnancy and breastfeeding (red = contraindicated, amber = warning/precaution, green = indicated). Recommendations shown here are paraphrased for brevity: always consult your local labelling

[a] Includes interferon β_{1a} (formulations for both s.c. and i.m. injections), and interferon β_{1b} (s.c. injections)

[b] Statement made for all formulations of interferon β

[c] Similar statements are made in US Prescribing Information for s.c. interferon β_{1a} and interferon β_{1b}, but no such statement is made for i.m. interferon β_{1a}

therefore, dimethyl fumarate has not been associated with adverse pregnancy outcomes.

Interferon β Pregnancy outcomes with interferon β have been collected in major registries, namely the Italian Multiple Sclerosis Register (88 exposed and 308 unexposed pregnancies) [28, 34], the German Multiple Sclerosis and Pregnancy Registry (251 exposed and 194 unexposed pregnancies) [35], the Merck KGaA Global Drug Safety Database (1022 exposed pregnancies) [36], and a Nordic Pregnancy Registry (875 exposed pregnancies, 1831 unexposed pregnancies) [37]. Together, these studies showed that there was no excess risk to the foetus resulting from exposure in utero to interferon β, with regard to rates of live births, spontaneous abortions, or congenital abnormalities; the frequency of these outcomes was comparable to those observed in the general population. Mean birth weight and birth length were also consistent between neonates exposed or not exposed to interferon β in utero [35, 37].

Teriflunomide and leflunomide An analysis of the global pharmacovigilance database for this agent found a rate of spontaneous abortion of 19% among 70 pregnancies with known exposure to teriflunomide, which was described as being within the range of rates expected for the general population (40% of these women underwent elective terminations of the pregnancy) [38]. There were no congenital abnormalities in 26 live births. Most of the women who carried the pregnancy to term underwent the rapid elimination procedure for teriflunomide (23/26, 88%). A more recent (up to December 2017) survey of 437 teriflunomide-exposed pregnancies (220 with known outcomes) found a rate of spontaneous abortion of 21% [39]. There were four birth defects (one considered major). These outcomes were again considered consistent with those expected from the general population, without demonstration of a teratogenic signal for teriflunomide.

The analysis from the global pharmacovigilance database for teriflunomide also documented no adverse birth outcomes from 22 pregnancies of partners of male patients taking teriflunomide [38]. Similar results were found from a recent analysis of 232 pregnancies exposed to teriflunomide or leflunomide [40]. The ongoing International Teriflunomide Pregnancy Exposure Registry is aiming to recruit 196 women with pregnancies exposed to teriflunomide (with at least 104 live births) from 17 countries [41]. This population will provide 80% power to detect a 3.95-fold increase in the risk of birth defects associated with teriflunomide exposure compared with rates from the EUROCAT database.

Leflunomide, which acts as a prodrug for teriflunomide, has been in clinical use for arthritis for about 2 decades. Of 587 leflunomide-exposed pregnancies with known outcome, the rate of birth defects was 7%, with the majority being minor birth defects [42]. According to the authors, these data suggested a lack of teratogenic potential for leflunomide, consistent with experience with teriflunomide, discussed above.

"High-efficacy" DMDs

Alemtuzumab A total of 179 pregnancies occurred in 131 women treated with alemtuzumab in randomised clinical trials in a report from 2015 [43]. Although the number of pregnancies was limited, these data suggested a similar frequency of spontaneous abortions between women who had received alemtuzumab and women in the general population. No congenital abnormalities were observed in these offspring. An updated report from 2017 (248 pregnancies) provided similar conclusions [44].

Cladribine tablets Forty-four pregnancies occurred in women exposed to cladribine tablets and 20 pregnancies occurred in placebo-treated women during the clinical development of cladribine tablets in MS. Outcomes were similar in each group for live births (41% vs. 45%, respectively) and spontaneous abortion (21% vs. 25%); rates of elective termination were 32% vs. 20%, respectively [45].

Fingolimod A recent study of prospective data was reported from the Multinational Gilenya® Pregnancy Exposure Registry (prospective) and the Novartis Safety database (NSDB), which includes the PRegnancy outcomes Intensive Monitoring (PRIM) programme [46]. Rates of congenital malformations in 1586 fingolimod-

exposed pregnancies were within the expected range for the general population. The rate of spontaneous abortion was 7.4% in the Registry, 8.1% in the NDSB, and 13.1% in PRIM. These were all within the expected range for this outcome cited for the general population of 7–20%, and the authors emphasised methodological differences likely contributed to the differences between the three databases. However, a recent survey of data by the European Medicines Agency has found a doubling of rates of major congenital malformations in offspring of mothers exposed vs. not exposed to fingolimod, which underpins the current contraindication for fingolimod in pregnancy [47]. It is important to avoid reactivation of disease activity in patients who discontinue fingolimod (see below).

Natalizumab Data from a registry in Germany were used to compare pregnancy outcomes among three groups of women: 101 women with RRMS with pregnancy exposed to natalizumab in the first trimester (72 live births), 78 women with RRMS with pregnancies not exposed to natalizumab, although they may have received treatment with other DMDs (69 live births), and a healthy control group of 97 women without MS (92 live births) [48]. There were no significant differences between groups for rates of major malformations, birth weight < 2500 g, or premature birth. There were significantly more miscarriages in the groups with MS and average birth weights were lower compared with the healthy group, although there were no significant differences between patients with RRMS who had been exposed or not exposed to natalizumab. In another observational study, a multivariable analysis reported an increased rate of miscarriage in women who had received natalizumab compared with other DMDs (odds ratio 3.9, $p < 0.001$), although the observed rate did not exceed the range of rates reported for the general population; there was no increased risk of foetal malformations with natalizumab [49]. However, the global Tysabri Pregnancy Exposure Registry did not find excess miscarriages or birth defects associated with pregnancies exposed to natalizumab, compared with the general population and based on 376 pregnancies [50]. A recent retrospective chart review that included data on 15 infants born to 13 mothers with MS who were treated with natalizumab in the third trimester concluded that haematological abnormalities may occur in one-third of infants exposed to natalizumab during the third trimester, but that the treatment was generally safe [51]. Withdrawal of natalizumab is also associated with potential for disease reactivation (see below).

Ocrelizumab Outcomes from 267 pregnancies in women with MS who became pregnant while receiving ocrelizumab have been reported [52]. For exposed vs. unexposed pregnancies, there were similar rates of spontaneous abortion (4% vs. 3%), and the proportion of live births was similar once a higher proportion of elective terminations in the ocrelizumab-exposed group was considered.

CONSENSUS RECOMMENDATIONS ON THE USE OF DMDS DURING PREGNANCY AND BREASTFEEDING

Women Planning a Pregnancy

The evidence summarised above has demonstrated a low risk of adverse pregnancy outcomes in patients who became pregnant while taking most DMDs. This information is useful for counselling and reassuring patients who become pregnant while taking a DMD who decide to take their pregnancy to term. Nevertheless, the number of exposed pregnancies is low for most DMDs at this time, except for the large database of clinical experience gained with interferon β in this setting during decades of therapeutic use; in general, the current contraindications in the labelling for current DMDs should be respected.

General principles for making treatment decisions when a woman with MS is planning a family is planning a family are shown in Table 2 and Fig. 1, and our consensus on which DMDs are suitable for patients with different levels of MS disease activity is shown in Table 3. The group recommends that a patient needs to be in remission for at least 1 year prior to pregnancy planning to avoid any potential risk of disease

Table 2 Summary of authors' recommendations for the use of DMDs in advance of, during, and in the postpartum period

	In advance of pregnancy	During pregnancy, or if unplanned pregnancy is discovered	postpartum/breastfeeding
Possible use during pregnancy			
Interferonβ	Safe to continue into pregnancy if clinically needed		Safe to breastfeed on treatment
Glatiramer acetate	Generally considered safe in pregnancy, use if benefits to mother outweigh risk to foetus		Breastfeed on treatment only if benefits clearly outweigh risks
Natalizumab[a]	Option for patient with high disease activity planning a pregnancy	Can be used up to 30 weeks' gestation for a patient with high MS activity	Do not breastfeed during treatment
Dimethyl fumarate	Short half life facilitates withdrawal	Not recommended, use only if benefits clearly outweigh risks	Breastfeed on treatment only if benefits clearly outweigh risks
Contraindication during pregnancy			
Fingolimod[a,b]	2 months washout before pregnancy should begin	Contraindicated – withdraw treatment	Do not breastfeed during treatment
Teriflunomide	Consider switch to alternative DMD if patient plans pregnancy soon (use rapid elimination procedure)	Contraindicated – stop treatment and use rapid elimination procedure	Do not breastfeed on treatment
Alemtuzumab[c]	4 months washout before pregnancy should begin	Use only if benefits clearly outweigh risks	Do not breastfeed for 4 months after the last dose
Cladribine tablets[c]	6 months washout before pregnancy should begin	Contraindicated, withdraw any current treatment if pregnancy occurs	Do not breastfeed for 10 days after the last dose
Ocrelizumab	12 months washout before pregnancy should begin	Avoid during pregnancy unless potential benefit to the mother outweighs potential risk to the foetus	Discontinue breast-feeding while receiving ocrelizumab

[a] Risk of rebound activation of MS disease activity if treatment is withdrawn; consider bridging with another DMD that is safe to use in pregnancy, e.g. interferon β

[b] Contraindications also apply to siponimod, which is not indicated for use in relapsing–remitting multiple sclerosis in Europe (the washout period for siponimod is 10 days)

[c] Alemtuzumab and cladribine tablets are hypothesised to act as immune reconstitution inhibitors, which may provide an opportunity for longer-term planning of a pregnancy free of DMD treatment or MS disease activity for the majority of patients (see text). Recommendations are compiled from labelling of DMDs, published articles, (see text for references) and authors' clinical experience

reactivation when DMDs are discontinued. A patient with active MS disease requires treatment. Interferon β is a rational option at this time, especially for a patient with low disease activity, given its indication for use in pregnancy. Glatiramer acetate is an alternative option, although its labelling does not provide strong support for use during pregnancy (see Table 1). A weaker consensus supported the use of dimethyl fumarate in a woman planning pregnancy, as the short half life of this agent facilitates switching at the time a pregnancy occurs. Alternatively, a patient with a low level of disease activity has the option of delaying treatment for a year to complete a pregnancy.

The care of women with high disease activity, which usually requires a high-efficacy DMD, involves a trade-off between protecting the patient from relapses and MS progression and minimising the risk of exposure of an unplanned pregnancy to treatment. For women with high MS disease activity planning pregnancy, the consensus supported the use of natalizumab with no washout period, while different washout periods from the last dose are required when using alemtuzumab, ocrelizumab, and cladribine tablets for women with high MS disease activity planning pregnancy (below, and Table 1). The absolute contraindications to the use of teriflunomide and fingolimod (and siponimod) during pregnancy should be respected for a patient with any level of disease activity in the absence of new data confirming their safety (Tables 1, 2).

It is important to note that alemtuzumab and cladribine tablets are hypothesised to act as immune reconstitution therapies (IRT), where short treatment courses given over 2 years

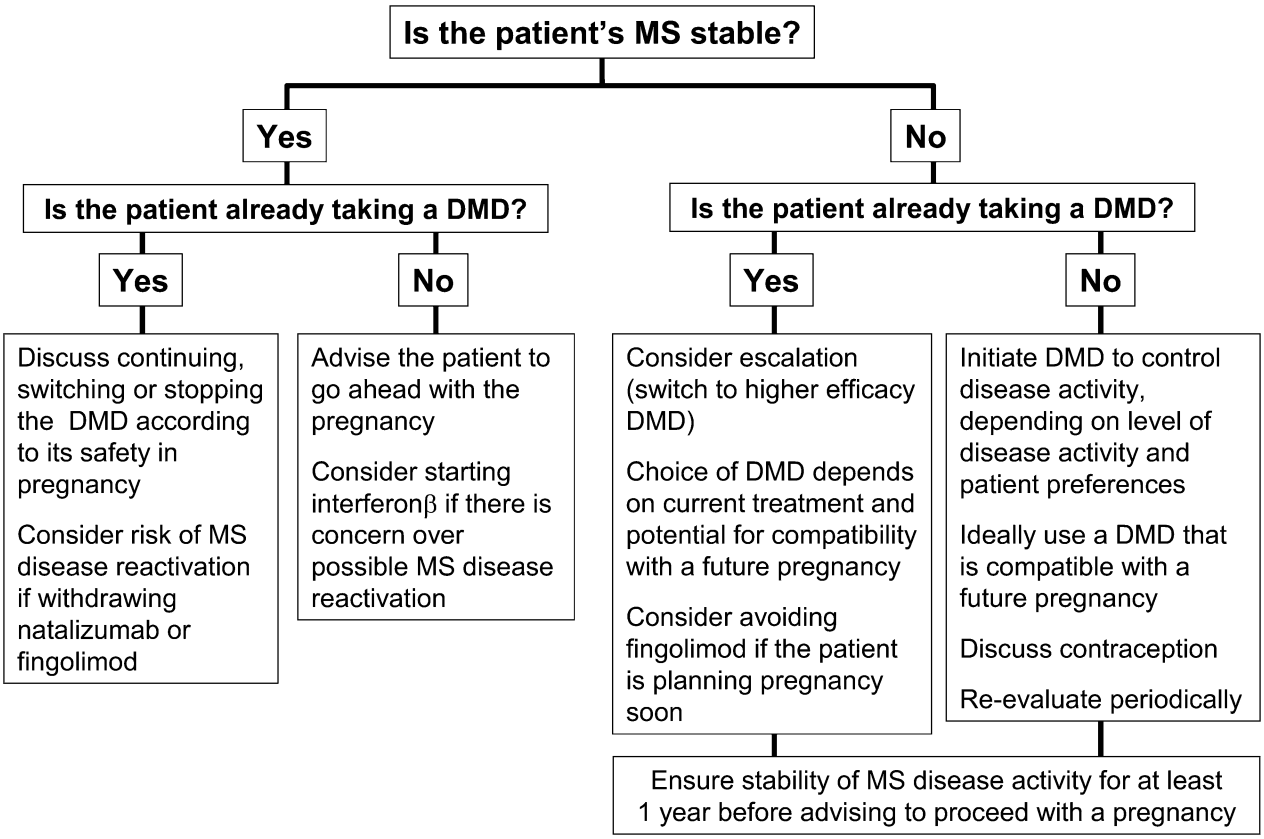

Fig. 1 Practical considerations relating to reviewing treatment of a woman with MS who is planning pregnancy

provide durable freedom from disease activity for a substantial proportion of patients [53]. Alemtuzumab can, in principle, be administered during pregnancy, according to its European label, although safety concerns unrelated to pregnancy have now limited its use [54], and treatment with cladribine tablets is contraindicated during pregnancy (Table 1). If the patient is prepared to delay her pregnancy for 4–6 months after the last dose of the IRT, this approach may provide a window of opportunity to complete a pregnancy uncomplicated by either recurrence of disease activity or concomitant DMD administration.

Unplanned Pregnancy While Taking a DMD for MS

About half of all pregnancies worldwide are unplanned [55]. Most DMDs should be discontinued immediately on discovering a pregnancy, with the following possible exceptions, based on the literature and our clinical experience. Treatment with interferon β (and perhaps glatiramer acetate) can be continued if required clinically (see above). Where active treatment must be maintained, bridging between prior and subsequent higher activity DMDs with interferon β may be an option. A patient already taking natalizumab is likely to have high disease activity prior to natalizumab institution and will be at risk of reactivation of MS disease activity if treatment is withdrawn (see above). We recommend the use of natalizumab in a pregnant patient with high disease activity

Table 3 Expert consensus recommendations on the use of individual disease-modifying drugs (DMDs) in women planning a pregnancy according to disease activity

Patient with active MS	Patient with highly active MS
High consensus	High consensus
Interferon β	Cladribine tablets
Glatiramer acetate	Natalizumab
	Ocrelizumab
Moderate consensus	Moderate consensus
Dimethyl fumarate	Alemtuzumab
Cladribine tablets	
Low consensus	Low consensus
Natalizumab	Dimethyl fumarate
Ocrelizumab	

Consensus levels were as follows: high, 8 or more physicians; moderate, 4–7 physicians; low, 1–3 physicians

requiring continued treatment, usually continuing until up to week 30 of the pregnancy, based on individual patient considerations (the use of natalizumab in the third trimester has been associated with transient mild-to-moderate thrombocytopenia and anaemia in the neonate [56]). Natalizumab can be given at 6-weekly intervals, instead of the usual 4-weekly doing interval, if reducing the intensity of treatment is considered helpful.

Discontinuing a DMD and Avoiding Rebound MS Activation

Washout periods vary between different DMDs. As a general guide, based on labelling and clinical experience, we recommend the following intervals between withdrawal of DMDs and becoming pregnant (this list does not include those agents which can be continued into pregnancy if needed, see Table 2):

Alemtuzumab 4 months (but can be used in pregnancy if clinically justified).

Cladribine tablets 6 months.

Fingolimod 2 months.

Ocrelizumab 6–12 months.

Siponimod 10 days.

Teriflunomide: Plasma levels of teriflunomide must be < 0.02 mg/l before pregnancy can be initiated. Unaided, this takes 8 months, on average, but can be achieved in 11 days using the rapid elimination procedure [57, 58].

Marked increases in MS disease activity (clinical relapses and MRI lesions) have been observed in patients who have discontinued treatment with fingolimod or natalizumab, including when these drugs have been discontinued to facilitate a pregnancy [59–62]. A report from the pregnancy registry for fingolimod in Germany found that relapses during pregnancy were common among women who discontinued fingolimod before they became pregnant (28% of 46 women) and among women who discontinued fingolimod after a positive pregnancy test (24% of 110 women) [63]. Data from a registry based in Kuwait showed that the risk of relapses during pregnancy and postpartum was higher than had been assumed previously (17% and 14%, respectively) and that the highest rate of relapses occurred in patients previously managed on fingolimod and natalizumab [64].

Lymphopenia occurring during the first 3 months of treatment with fingolimod has been proposed as a possible marker of patients at most risk of MS reactivation following withdrawal of this agent [60]. Higher disease activity and longer duration of MS were described as risk factors for disease reactivation following withdrawal of natalizumab [65]. A longer washout period before pregnancy predicted a higher risk of relapse following withdrawal of fingolimod or natalizumab [60, 64]. Figure 2 shows consensus recommendations for avoiding disease reactivation in patients receiving fingolimod or natalizumab who are or intend to become pregnant based on the considerations discussed above.

Breastfeeding

Women are at increased risk of relapses during the postpartum period, but this risk must be balanced with the need to support and encourage women who wish to breastfeed their

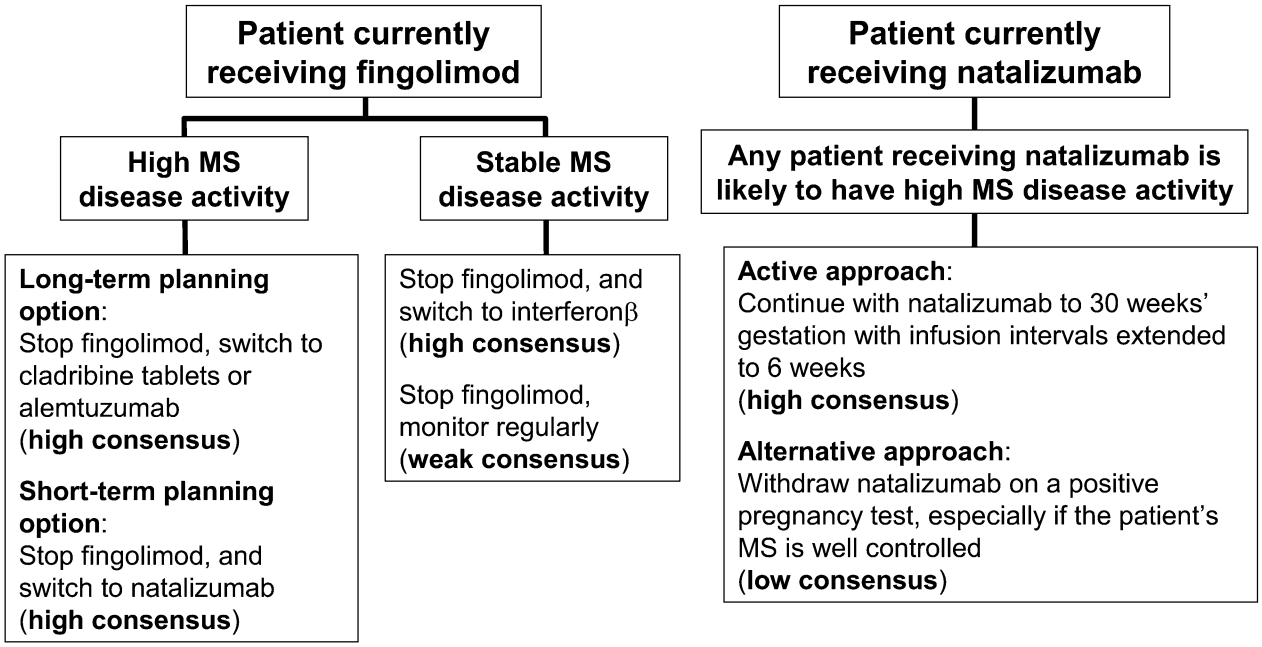

Fig. 2 Consensus recommendations on avoiding rebound MS disease activity in patients receiving fingolimod or natalizumab who are or intend to become pregnant. "High" or "stable" disease activity is defined arbitrarily based on the presence or absence of MS disease activity during the preceding year

child. In the authors' experience, most neurologists are willing to maximise options for breastfeeding, providing disease activity can be controlled (see Table 2). The absence of disease activity during pregnancy and in MRI follow-up performed following delivery may encourage a period of breastfeeding if the mother is willing to do so. If a relapse occurred during pregnancy or radiological activity appeared, it is recommended to resume the DMD after delivery. The European label for interferon β supports its use during breastfeeding, with qualified support for glatiramer acetate, and alemtuzumab only at this time (Table 1). US labels for all DMDs provide a general instruction to balance benefits and risks, except for contraindications for teriflunomide and cladribine tablets.

MANAGING RELAPSES DURING PREGNANCY

Corticosteroids are the mainstay of treatment for MS relapses, including during pregnancy [15], but are weakly teratogenic, with an increased risk of cleft palate when used in the first trimester (odds ratio 3.5) [66]. Intravenous immunoglobulin (IVIg) is considered safe for use during breastfeeding, according to the European label for an IVIg product, as immunoglobulins pass naturally from mother to child via breast milk [67]. There is some evidence that IVIg may reduce the rate of relapses during pregnancy and the postpartum period [68], although the recent consensus statement from the UK does not support [15]. Plasma exchange may be considered for severe or disabling relapses that do not respond to corticosteroid treatment [15, 69]. Evidence supporting the use of plasma exchange in less severe cases is lacking, however, and this intervention may increase the risk of hemodynamic instability and central line infection and thrombosis [69].

CONCLUSIONS AND SUMMARY OF RECOMMENDATIONS

Managing MS in women considering, or already embarked on, a pregnancy is a challenging balancing act between protecting the patient from MS activity and progression and avoiding unnecessary exposure of the foetus to DMDs. In addition, data on the efficacy and safety of most individual DMDs are limited for this population. Exceptions to this include interferon β and glatiramer acetate (which are relatively well studied and likely to be safe for use in pregnancy) and DMDs with outright contraindications in this setting (which should never be used in pregnancy). Table 2 summarises our recommendations for DMD treatment for a patient in advance of pregnancy, during pregnancy, and postpartum. These were based to an important extent on US and European labelling. This is a fast-moving field, however, and regulatory labels may be slow to catch up with the clinical evidence base. We have also brought our clinical experience to bear here, as leading physicians in Gulf states. Guidance on the selection of DMD treatment according to disease activity for this population has been particularly lacking in current guidance, and we have sought to provide pragmatic recommendations on this.

Care should be taken to withdraw a DMD that is unsafe for use in pregnancy in good time for its potentially adverse effects to dissipate. Where possible, switching a patient to a DMD that is known to be relatively safe during pregnancy provides a rational option for these patients, especially as many pregnancies are unplanned. The recent change to the indication for interferon β, permitting use in pregnancy where clinically needed and removing obstacles to its use during breastfeeding, has broadened the options for maintaining DMD therapy at this time beyond glatiramer acetate. Natalizumab (for patients with high disease activity) may also be continued into a pregnancy, although a patient taking natalizumab should not breastfeed. The use of DMDs hypothesised to act as IRTs (currently alemtuzumab and cladribine tablets) may provide a period of stable disease without maintenance treatment that provides an opportunity to embark on long-term planning for a pregnancy. However, the patient should be prepared to wait for up to 20 months (cladribine tablets) before becoming pregnant.

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Data AvailabilityData Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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