DISEASE-MODIFYING DRUGS

(DMDs) and Family Planning In Multiple Sclerosis (MS)

Selection of DMDs for MS while planning a family:

Consensus from the Arabian Gulf

Guidance for healthcare professionals addressing the treatment of multiple sclerosis in the Arabian Gulf countries

GULF-NONNI-00004

INTRODUCTION

The majority of people who develop MS are women. A marked increase in the prevalence of MS in most countries has further increased the number of women who develop MS at a time they are likely to consider planning a family. These trends in the epidemiology of MS are evident in the Gulf region, as elsewhere.

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.

MS has no adverse impact per se on a woman's fertility or a pregnancy; conversely, pregnancy has no long-term impact on the course of MS.

Nevertheless, the onset of MS has an impact on reproductive choices. The diagnosis of MS leads to fear and a feeling to uncertainly, and subsequently fewer pregnancies than they expected to have, had they not developed MS.

Pregnancy also impacts the management of MS. This is because women with MS commonly stop taking their DMD due to the fear of potential adverse effects of treatment on their pregnancy.

Most DMDs are contraindicated in pregnancy. The management of MS is especially challenging during pregnancy. This is because the withdrawal of DMDs leaves the patient at a risk of increased disease activity.

This article discusses recommendations by experts from the Arab Gulf on the application of DMD-based therapy for MS during pregnancy in the Gulf

- The recommendations are based on the impact of low or high levels of MS disease activity on the management.
- The efficacy, safety/tolerability, and monitoring burdens of individual DMDs are key aspects to consider when prescribing a DMD, irrespective of pregnancy status or plans.

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CONSENSUS RECOMMENDATIONS ON THE USE OF DMDs DURING PREGNANCY AND BREASTFEEDING

Need for active treatment of MS during pregnancy

01

There is a low risk of adverse pregnancy outcomes in patients who became pregnant while taking most DMDs.

02

This information is helpful to counsel and reassure patients who become pregnant while taking a DMD who decide to take their pregnancy to term.

03

In general, the current contraindications in the labelling for current DMDs should be respected.

04

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 reactivation when DMDs are discontinued.
A patient with active MS disease requires treatment.

05

A patient with a low level of disease activity has the option of delaying treatment for a year to complete a pregnancy.

06

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.

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SUMMARY OF AUTHOR'S 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			
Interferonß	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 during 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. interferonß

[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.

(red = contraindicated, amber = warning/precaution, green = indicated)

PRACTICAL CONSIDERATIONS RELATING TO REVIEWING TREATMENT OF A WOMAN WITH MS WHO IS PLANNING PREGNANCY

Is the patient's MS stable?

Yes

Is the patient already taking a DMD?

Yes

Discuss continuing, switching or stopping the DMD according to its safety in pregnancy

Consider risk of MS disease reactivation if withdrawing natalizumab or fingolimod

No

Advise the patient to go ahead with the pregnancy

Consider starting interferon ß if there is concern over possible MS disease reactivation

No

Is the patient already taking a DMD?

Yes

Consider escalation (switch to higher efficacy DMD)

Choice of DMD depends on current treatment and potential for compatibility with a future pregnancy

Consider avoiding fingolimod if the patient is planning pregnancy soon

Initiate DMD to control disease activity, depending on level of disease activity and patient preferences

Ideally use a DMD that is compatible with a future pregnancy

Discuss contraception

Re-evaluate periodically

Ensure stability of MS disease activity for at least 1 year before advising to proceed with a pregnancy

No

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EXPERT CONSENSUS RECOMMENDATIONS ON THE USE OF INDIVIDUAL DMDS IN WOMEN PLANNING A PREGNANCY ACCORDING TO DISEASE ACTIVITY

Most DMDs should be discontinued immediately on discovering a pregnancy. Where active treatment must be maintained, bridging between prior and subsequent higher activity DMDs with interferon may be an option.

Patient with active MS		Patient with highly active MS
High consensus		**High consensus**
Interferon ß		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

DISCONTINUING A DMD AND AVOIDING REBOUND MS ACTIVATION

Washout periods vary between different DMDs. Based on labelling and clinical experience, the following intervals were recommended between withdrawal of DMDs and becoming pregnant. This list does not include those agents which can be continued into pregnancy if needed, see Table 1)

Alemtuzumab

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

Cladribine tablets

6 months

Fingolimod

2 months

Siponimod

10 days

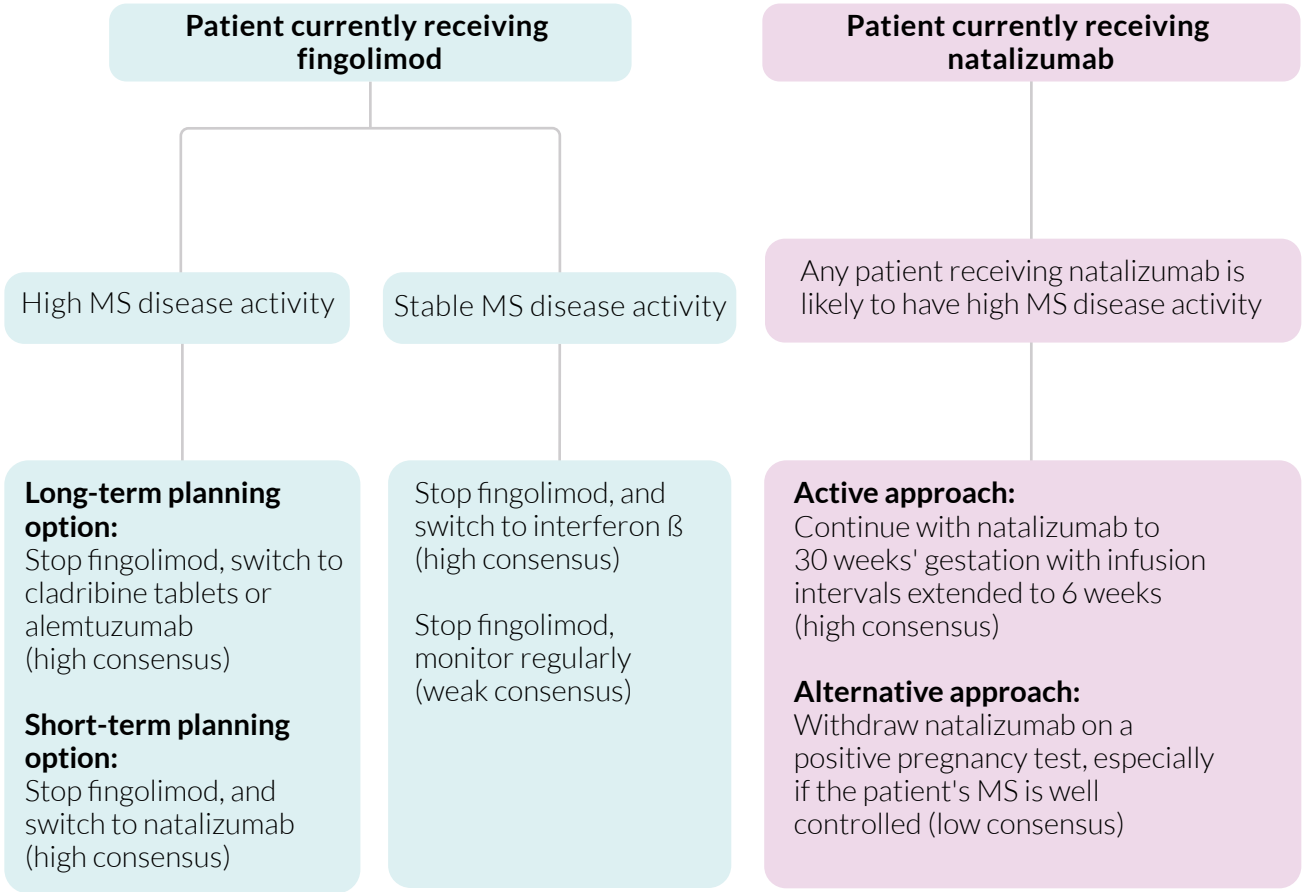
Ocrelizumab

6-12 months

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 the withdrawal of this agent

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

CONSENSUS RECOMMENDATIONS ON AVOIDING REBOUND MS DISEASE ACTIVITY IN PATIENTS RECEIVING FINGOLIMOD OR NATALIZUMAB WHO ARE OR INTEND TO BECOME PREGNANT



BREASTFEEDING

In the authors' experience, most neurologists are willing to maximise options for breastfeeding, providing disease activity can be controlled.

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 ß supports its use during breastfeeding, with qualified support for glatiramer acetate, only at this time.

SUMMARY OF RECOMMENDATIONS

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 ß 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 ß or natalizumab after an appropriate washout period for women who become pregnant on fingolimod.

REFERENCE

Alroughani, R., Inshasi, J., Al-Asmi, A. et al. Disease-Modifying Drugs and Family Planning in People with Multiple Sclerosis: A Consensus Narrative Review from the Gulf Region. ***Neurol Ther*** (2020).

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