



Review

# Saudi Consensus Recommendations on the Management of Multiple Sclerosis: Family Planning within the Management of MS

Mona M. Al-Khawajah <sup>1</sup>, Rayan G. Al-Barakati <sup>2</sup>, Ahmed H. Al-Jedai <sup>3</sup>, Yaser M. Al-Malik <sup>4,5</sup>, Hajer Y. Al-Mudaiheem <sup>3</sup>, Bedor A. Al-Omari <sup>6</sup>, Ibtisam A. Al-Thubaiti <sup>7</sup>, Rumaiza H. Al-Yafeai <sup>8</sup>, Reem F. Bunyan <sup>9</sup>, Edward J. Cupler <sup>10</sup>, Mohammed Hakami <sup>11</sup>, Hanaa M. Kedah <sup>12</sup>, Seraj Makkawi <sup>13,14,15</sup>, Leena H. Saeed <sup>16</sup>, Jameelah A. Saedi <sup>17</sup>, Eslam Shosha <sup>18</sup> and Mohammed A. Al-Jumah <sup>19,\*</sup>

- <sup>1</sup> Neuroscience Center, King Faisal Specialist Hospital and Research Center, Riyadh 11211, Saudi Arabia
- <sup>2</sup> Department of Obstetrics and Gynecology, Majmaah University, Al-Majmaah 11952, Saudi Arabia
- <sup>3</sup> Deputyship of Therapeutic Affairs, Ministry of Health, Riyadh 12382, Saudi Arabia
- <sup>4</sup> College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Prince Mutib Ibn Abdullah Ibn Abdulaziz Rd., Ar Rimayah, Riyadh 14611, Saudi Arabia
- <sup>5</sup> Division of Neurology, King Abdulaziz Medical City (National Guard Health Affairs), Riyadh 14815, Saudi Arabia
- <sup>6</sup> Department of Pharmacy, Prince Sultan Military Medical City, Saudi Society of Clinical Pharmacy (SSCP), Riyadh 11159, Saudi Arabia
- <sup>7</sup> Department of Neurology, King Fahad Military Medical Complex Dhahran, Abqaiq Road, Dhahran 31932, Saudi Arabia
- <sup>8</sup> Department of Neurology, Psychiatry and Psychology, My Clinic International Medical Co., Prince Sultan Road Al Mohammadiyyah, Jeddah 21411, Saudi Arabia
- <sup>9</sup> Department of Neurology, King Fahad Specialist Hospital Dammam, Ammar Bin Thabit Street, Dammam 32253, Saudi Arabia
- <sup>10</sup> Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Jeddah 21499, Saudi Arabia
- <sup>11</sup> Neurology Unit, King Fahad Central Hospital, Abu Arish Road, Jazan 82666, Saudi Arabia
- <sup>12</sup> Department of Neurology, Hera General Hospital, Al Buhayrat, Makkah 21955, Saudi Arabia
- <sup>13</sup> College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Mecca Jeddah Highway, Jeddah 22384, Saudi Arabia
- <sup>14</sup> King Abdullah International Medical Research Center, Prince Nayef Street, Jeddah 23816, Saudi Arabia
- <sup>15</sup> Department of Medicine, Ministry of the National Guard-Health Affairs, Palestine Bani Malik, Jeddah 23235, Saudi Arabia
- <sup>16</sup> Department of Pharmacy, King Fahad Medical City, Riyadh 11525, Saudi Arabia
- <sup>17</sup> Department of Neurology, King Abdullah Bin Abdulaziz University Hospital, King Khalid International Airport, Riyadh 11564, Saudi Arabia
- <sup>18</sup> Division of Neurology, Department of Medicine, McMaster University, 1280 Main St. W, Hamilton, ON L8S 4L8, Canada
- <sup>19</sup> Department of Neurology, King Fahad Medical City, Riyadh 11525, Saudi Arabia
- \* Correspondence: jumahm@gmail.com



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**Abstract:** This review article addresses the complex issues faced by individuals with Multiple Sclerosis (MS) who are planning a family, becoming pregnant, or wishing to breastfeed their baby. Recommendations and guidelines were discussed and agreed upon by neurologists, neuroradiologists, nurses, and pharmacists involved in the management of MS in the Kingdom of Saudi Arabia (KSA). MS itself does not harm a pregnancy, and people with MS of childbearing age can be encouraged to enjoy family life. Family planning should be a part of the initial conversation with a newly diagnosed patient of childbearing age. Interferons and glatiramer acetate can be continued throughout pregnancy and can be administered during breastfeeding if the benefits outweigh the risks. These DMTs may be considered for a woman with well-controlled MS who is planning a pregnancy or otherwise not using contraception, according to an individualized risk-benefit analysis. The use of contraception should be maintained during the administration of other disease-modifying therapies (DMTs). Natalizumab can be administered at a reduced administration frequency to women

with high MS disease activity up to 30 weeks gestation (this agent may induce hematological abnormalities in the fetus). Other DMTs should be withdrawn for variable periods before contraception is stopped and immediately after the discovery of a pregnancy (beware of rebound disease activity after withdrawing natalizumab or fingolimod). Resumption of treatment should not be delayed in women at risk of relapse during the postpartum period and especially in those who do not wish to breastfeed.

**Keywords:** multiple sclerosis; pregnancy; family planning; contraception; breastfeeding

## 1. Introduction

Raising a family is an important goal in life for most people in Saudi Arabia and raising large families is common [1]. Most patients with new-onset multiple sclerosis (MS) in Saudi Arabia receive their diagnosis before the age of 40 years, which is consistent with clinical experience elsewhere [2,3]. Accordingly, a substantial proportion of patients with MS in Saudi Arabia are of an age where they will be planning or raising a family. Multiple sclerosis per se does not appear to be harmful to the course of a pregnancy, with no evidence of increased risk of infertility, adverse pregnancy outcomes, or adverse neonatal outcomes associated with the condition [4,5]. Indeed, recent evidence shows that women of childbearing age diagnosed with MS can normally conceive and breastfeed [5]. Moreover, many patients with mild disease do not require treatment before, during, or after pregnancy [5]. However, although MS has not been found to affect fertility or pregnancy, research has shown that the disease has been associated with a considerably high prevalence of issues such as sexual dysfunction (as high as 62.5%) worldwide [6]. Women with MS often demonstrate significantly lower female sexual function index scores in comparison with healthy subjects [7]. Concerns about the possible adverse effects of MS (or its treatment) on pregnancy have led women in the Middle East and elsewhere to either delay or even abandon their ambitions to raise a family [8–10].

There are contraindications and precautions related to most disease-modifying therapies (DMTs) for MS that complicate the management of MS. Since many DMTs for MS are contraindicated during pregnancy and because the frequency of MS relapses decreases to some extent during the second and third trimesters of pregnancy [11], MS medications could be discontinued during pregnancy. However, in some cases, DMTs during pregnancy may be considered based on disease activity and an individualized risk-benefit analysis (e.g., for patients with highly active disease, potential adverse effects on the fetus). The possibility of increased MS disease activity in the months following delivery must also be considered, along with tailoring individualized treatment to accommodate wishes to breastfeed the infant, where possible [4,12].

Women with MS and their partners should be supported in their desire to pursue a family life. This article summarizes the recommendations in the new Saudi consensus on the management of individuals with MS who are planning a family, who are already pregnant, or who wish to breastfeed. A panel of professionals specialized in the treatment of MS including neurologists, neuroradiologists, MS nurses, and pharmacists congregated to review the latest relevant medical literature and bring forward applicable evidence-based recommendations.

## 2. Multiple Sclerosis and Fertility

Multiple Sclerosis does not seem to affect male fertility based on preliminary studies on relapsing-remitting multiple sclerosis that showed no deterioration in gonadal steroids and the quality of sperm [13]. Similarly, studies have shown that fertility in men with relapsing-remitting multiple sclerosis is not affected by the use of natalizumab and ocrelizumab [14].

In the absence of additional risk factors for an adverse pregnancy outcome, MS per se does not place a pregnancy into a “high-risk” category [4]. Indeed, MS has not been found

to impact fertility, the course of pregnancy, or fetal development [15,16]. Antenatal care follows the general recommendations, with the usual plan of dietary supplementation of folic acid, vitamins, minerals, and iron appropriate for a pregnant woman [17].

Consideration of the possibility of pregnancy should be part of the discussion on the management of MS when a patient of childbearing age is diagnosed with MS. In addition, pre-pregnancy counseling with their MS healthcare professionals should be repeated at regular intervals, especially if a DMT has already been prescribed, or is being considered. The desire to plan a family influences the choice of DMT. Table 1 summarizes the properties of the available DMTs relevant to family planning.

**Table 1.** Properties of disease-modifying therapies for multiple sclerosis relevant to a patient planning a family from the Ministry of Health Product Information, US FDA Label Information, and the Electronic Medicines Compendium.

	Known Risk of Teratogenicity	Washout Period before Stopping Contraception	Use during		Risk of Rebound Disease Activity
			Pregnancy	Breastfeeding	
Interferons [18]	Low <sup>a</sup>	Washout not needed	Yes <sup>b</sup>	Yes <sup>b</sup>	No
Glatiramer acetate [19]	Low or absent <sup>c</sup>	Washout not needed	Yes <sup>b</sup>	Yes <sup>b</sup>	No
Teriflunomide	Yes	Use accelerated elimination procedure <sup>d</sup>	No	No	No
Dimethyl fumarate	Limited data	Discontinue before or at time contraception is stopped	No	No	No
Natalizumab	Limited data	No	Yes <sup>e,f</sup>	Limited Data <sup>g,h</sup>	Yes
Fingolimod	Yes	2 months <sup>h</sup>	No	No	Yes
Siponimod	Yes	10 days	No	No	Limited data
Ocrelizumab [20]	Limited data	6 months <sup>i</sup>	Limited data	Limited data <sup>g</sup>	No
Rituximab [21]	Limited data	6 months <sup>i</sup>	Limited data	Limited data <sup>g</sup>	No
Alemtuzumab [22]	Limited data	4 months <sup>h</sup>	No	No	No
Cladribine tablets [23]	Yes	6 months (both men and women) <sup>h</sup>	No	No	No

<sup>a</sup> "A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy" (European Summary for product Characteristics SmPC for Rebif®); <sup>b</sup> Can be used if benefits outweigh risks. <sup>c</sup> Current data on pregnant women indicate no malformative or fetoneonatal toxicity of Copaxone. (SmPC for Copaxone®); <sup>d</sup> Accelerated elimination procedure to rapidly achieve teriflunomide plasma concentrations < 0.02 mg/L. <sup>e</sup> Natalizumab can be used with great care (6–8 weeks dosing) up to 30 weeks of pregnancy, if needed. <sup>f</sup> In cases of third-trimester exposure to natalizumab, neonatal monitoring for hematologic abnormalities (anemia and thrombocytopenia), and their complications should be performed. <sup>g</sup> A decision to use during breastfeeding should only be made after risk-benefit analysis, and if the benefits to use the medication outweigh the risk. <sup>h</sup> See the European summary of product characteristics for each drug. <sup>i</sup> Some data suggest 6–8 weeks.

There is no absolute contraindication to the use of interferons and glatiramer acetate during pregnancy, and these DMTs may be considered for a woman with well-controlled MS who is planning a pregnancy or otherwise not using contraception, according to an individualized risk-benefit analysis. Treatment with natalizumab can be continued up to 30 weeks gestation in women with highly active MS. Natalizumab should be administered at a reduced frequency (infusions reduced from monthly to every 6–8 weeks) to reduce exposure while maintaining efficacy. This is because natalizumab is known to be associated with a risk of rebounding MS disease activity when withdrawn [24]. Although natalizumab may be used in pregnancy for women with well-controlled disease activity, it is recommended to switch to Rituximab before discontinuing contraception to prevent rebound disease activity [25].

Other DMTs have a warning or absolute contraindication for use during pregnancy (Table 1). Pregnancy should be excluded before administering these agents, and a switch to

an alternative DMT (based on disease activity and an individualized risk-benefit analysis) would be required to facilitate family planning even when MS disease activity is well controlled. A washout period is required for most DMTs before contraception is stopped, and the duration of the washout period varies depending on the DMT used to ensure that the agent in question (and its pharmacologic effect) is cleared from the system.

The accelerated washout procedure for teriflunomide (described in its labeling) should be employed immediately after its discontinuation to rapidly achieve a plasma concentration level below 0.02 mg/L. Note that the withdrawal of Fingolimod is also known to be associated with rebound MS disease activity and can be severe and prolonged [26]. Therefore, a switch to an alternative DMT is recommended before stopping contraception (ideally a B-cell-depleting agent, such as rituximab) [20].

There is no clinically significant pharmacokinetic interaction between oral contraceptives and interferons, Glatiramer acetate, natalizumab, fingolimod, teriflunomide, ocrelizumab, or alemtuzumab. The European and US labeling of cladribine tablets suggests that women should add another barrier method to oral contraception (double contraception) during, and for 6 months after each treatment course, as the effect of this agent on concomitant contraception is not well understood.

### 3. Use of DMTs during Pregnancy

Since many pregnancies are unplanned, exposure to an ongoing DMT during the first trimester often occurs. In such cases, additional pregnancy monitoring might be needed for potential risks to the pregnancy or fetus. Recent evidence has shown no association between early pregnancy use of DMT and significant adverse outcomes in pregnancy [15]. Table 2 summarizes current expert opinions on the care of women who become pregnant on currently available DMTs. These findings are consistent with recommendations summarized and published by the American Academy of Neurology (2019) [5].

For all DMTs, patients should be counseled on the potential effects on pregnancy, and the development of the fetus should be monitored appropriately where there is potential for harm [27]. Well-controlled patients taking interferons, glatiramer acetate, or natalizumab, should have their neonates monitored for hematological abnormalities after delivery [28]. In addition, many patients do not require DMTs during pregnancy, although treatment with injectables such as interferon-beta and glatiramer acetate may be resumed [29]. Fingolimod, teriflunomide, and should be withdrawn once the pregnancy is discovered (monitor for rebound disease activity when withdrawing fingolimod and use the accelerated elimination procedure for teriflunomide). Interim results from an ongoing registry have shown that first-trimester exposure to dimethyl fumarate is not associated with worse outcomes [30] which is consistent with previous evidence [31]. Natalizumab and anti-CD20 agents (ocrelizumab and rituximab) may cause hematological abnormalities in the fetus; thus, appropriate neonatal screening should be performed [28]. Additionally, a systematic review found no increased risk of spontaneous abortion, congenital defects, or preterm delivery associated with the administration of interferons, glatiramer acetate, or natalizumab [32].

DMTs believed to act as immune reconstitution therapies (currently cladribine tablets and alemtuzumab) are not administered as continuous therapy and thus, cannot be “withdrawn” [33]. However, the next dose of these agents should be withheld until pregnancy is complete. The labeling of cladribine tablets states that a male patient should not get his partner pregnant for a period of 6 months following the last dose of this DMT [23].

**Table 2.** Expert recommendations on the care of women who get pregnant while taking disease-modifying therapies for multiple sclerosis.

	<b>Known/Documented Risks from 1st-Trimester Exposure</b>	<b>Recommended Actions to Take if Pregnancy Is Discovered while Receiving DMT Therapy *</b>
Interferons	None	- These DMTs are safe to use until pregnancy is confirmed and may be continued during pregnancy when needed clinically and after consideration of the individual risk-benefit
Glatiramer acetate	None	-
Teriflunomide	High risk for major and minor malformation, risk for preterm labor	- Discontinue immediately once patient is aware of the pregnancy - Accelerated elimination procedure immediately - Monitor closely for potential fetal malformations, preterm labor, and low birth weight - Patient should be counseled and made aware of the increased risk of teratogenicity
Dimethyl fumarate	Potential uncertain risk to fetus	- Discontinue once patient is aware of the pregnancy - Perform early ultrasound to detect any major malformation or potential risk for preterm labor.
Natalizumab	Risk of hematologic abnormalities in the fetus	- Refer to an MS specialist - Consider the risk of rebound MS disease activity on withdrawal - Can be continued up to 30 weeks gestation in patients with highly active disease - If natalizumab is continued during the third trimester, a neonatologist should be present at delivery to monitor for hematologic abnormalities (anemia and thrombocytopenia) and their complications.
Fingolimod	Potential risk of major malformation and preterm labor	- Withdraw immediately and monitor for rebound disease activity—consult an MS specialist if a rebound relapse occurs - Counsel patient on the increased risk of teratogenicity - Monitor for fetal malformations/potential preterm labor
Siponimod	Limited data available	- Monitor for fetal malformations/potential preterm labor
Ocrelizumab and rituximab	Limited data available	- Infant B-cell depletion is likely - Perform neonatal screening for B-cell depletion and pancytopenia

\* Consult an MS specialist for possible methods of preventing rebound during pregnancy or post-partum.

#### 4. Other Considerations during a Pregnancy for a Woman with Multiple Sclerosis

Magnetic resonance imaging (MRI) is generally not contraindicated at any time during pregnancy, but its use should be restricted to non-routine imaging for cases where the imaging results would impact clinical decisions. Gadolinium contrast media, in contrast, should be avoided during pregnancy, as it has been associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and stillbirth or neonatal death [34].

#### 5. Relapses during Pregnancy

Any woman with MS suffering a disabling relapse should be offered intravenous methylprednisolone at the recommended dose used in MS, regardless of the trimester, once an underlying infection, such as a urinary tract infection, has been excluded [27]. It is advised to treat only clinically significant relapses and avoid unnecessary treatment with methylprednisolone in the first trimester if possible [5]. Plasma exchange should be considered for extremely severe relapses that do not respond to corticosteroids [4].

## 6. Management of Symptoms of Multiple Sclerosis

There is little data available to guide symptomatic management during pregnancy. We recommend the following approaches to manage common and distressing/disabling symptoms of MS [5,35]:

### 6.1. Depression

Antidepressants, including tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), do not appear to be teratogenic and are generally considered safe. Sertraline should be considered for pregnant and nursing mothers.

### 6.2. Fatigue

Limited evidence exists on commonly used medications, such as amantadine, modafinil, and methylphenidate. Prescribing amantadine should be avoided during pregnancy because of possible teratogenicity. Modafinil and fampridine should be avoided for women who are trying to conceive, are pregnant, or are breastfeeding. A modest caffeine intake is an alternative approach to addressing fatigue.

### 6.3. Spasticity

Baclofen should not be prescribed during pregnancy (intrathecal baclofen may be a safe option). Baclofen is only secreted in small amounts in breast milk, and there is no specific recommendation regarding breastfeeding.

### 6.4. Neuropathic Pain

Gabapentin and pregabalin are safer than carbamazepine and baclofen. Additionally, the use of valproate or topiramate should be avoided in women who are trying to conceive or reliable birth control unless absolutely necessary.

## 7. Multiple Sclerosis and Management of Female Sexual Dysfunction

Detailed sexual history should be taken to identify any potential sexual dysfunction issues that the patient may be suffering from [36]. The most commonly used instrument is the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19) [37]. Collaboration between different healthcare providers, such as gynecologists, urologists, neurologists, psychiatrists, and psychotherapists can improve outcomes of sexual dysfunction management in MS patients [38]. DMTs have not been found to treat sexual dysfunction in Multiple Sclerosis. Data regarding the treatment of female sexual dysfunction is limited [39]. For instance, it is still unclear whether Sildenafil should be used or not due to conflicting results in the literature [40,41]. Patients with specific symptoms such as reduced lubrication can benefit from water-soluble lubricants and pelvic floor muscle training [42]. Sexual desire can improve using topical estrogen combined with methyl-testosterone [40]. It is also important to treat mood disorders such as depression if present to improve sexual function. However, it is important to take into consideration that the use of antidepressants such as SSRIs may cause an exacerbation of sexual dysfunction [43]. Therefore, cognitive behavioral therapy may be adopted as an effective treatment instead [44]. Moreover, antidepressants less likely to cause sexual side effects, such as Mirtazapine and Bupropion may also be considered [45]. Patients complaining of spasticity affecting sexual performance may benefit from baclofen, tizanidine, or benzodiazepines prior to sexual intercourse [46].

## 8. Multiple Sclerosis and Assisted Reproduction Technologies

Assisted reproduction technology (ART) may increase the risk of relapse in women with MS. Gonadotropin-releasing hormone (GnRH) antagonists may be a more appropriate option than a GnRH agonist, and the clinical outcomes following these approaches are similar, but a GnRH antagonist does not reduce estrogen levels, which may be protective in this setting [35,47].

## 9. Delivery and Postnatal Care

### 9.1. Delivery

The obstetrician will determine any need for induced labor or a cesarean section [5,48]. Epidural, peridural, caudal, spinal, subarachnoid, or intrathecal analgesia/anesthesia can be safely used in women with MS who are giving birth [35,48,49]. Benzodiazepines and/or an epidural anesthetic may be useful in controlling spasticity during labor. If a blood transfusion is required, irradiated blood products should be used for patients who have received alemtuzumab or cladribine tablets [4].

Loss of sensation associated with MS may reduce awareness of the onset of labor, especially where there is spinal cord involvement below T1. The patient should be advised to look out for other signs of labor onset, such as an increase in spasticity, gastrointestinal upset, flushing, and back pain [4].

### 9.2. Post-Partum Relapse and Disease Evolution

The risk of relapse in the postnatal period is correlated with the 12-month and 24-month annualized relapse rate preceding pregnancy [35]. Treatment should not be postponed and early reintroduction of DMTs may be recommended (as soon as the first 10 days postpartum), especially for women with high preconception disease activity and those who do not wish to breastfeed [50,51]. Clinical and radiological monitoring is recommended for patients who choose not to resume DMT [52]. Relapse itself should be managed as discussed above.

A recent retrospective study has shown that pregnancy and the post-partum period do not exacerbate disease progression; however, more studies are needed [53].

### 9.3. Breastfeeding

Women should be encouraged to breastfeed, as this is beneficial for the health of the mother and baby, as supported by the World Health Organization [51]. Some research has shown that breastfeeding has no impact on post-partum relapses while others have found that it is often associated with a lower risk of relapses after delivery [11,29]. When a woman wishes to breastfeed and the benefits outweigh the risks, she should opt for interferon gamma or glatiramer acetate, as biologically plausible risks to the infant with these drugs are exceedingly low [4]. Studies on monoclonal antibody exposure through breastfeeding have shown that monoclonal antibodies like natalizumab, ocrelizumab, or rituximab are safe to be continued during pregnancy [54]. However, the use of natalizumab during breastfeeding is still controversial as some studies have shown accumulation of the drug in breastmilk [55,56]. Note that interferon gamma is now indicated for use during breastfeeding when there is a clinical need [57], glatiramer acetate is permitted during breastfeeding when clinically indicated in the US and Europe, and natalizumab and ocrelizumab are contraindicated for use during breastfeeding in Europe but not in the USA. Fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, and cladribine are also contraindicated and must be discontinued during breastfeeding. Women should not breastfeed for one week after the last oral cladribine dose. Recent case reports have shown that the metabolite of dimethyl fumarate is transferred to breast milk in minimal doses [58]. If methylprednisolone was administered for relapse, women should be advised to wait 3–4 h before breastfeeding [59].

MRI with gadolinium is safe to use during breastfeeding due to the minimal distribution of gadolinium contrast agents into breast milk and the infant's gut [59,60].

## 10. Conclusions

With individualized management, support, and the use of evidence-based clinical decision recommendations, couples with partners suffering from MS should no longer abandon their wishes to raise a family. Expert assistance tailored to the needs of each couple can provide a smoother journey for patients across all stages of family planning, including pre-conception, pregnancy, and breastfeeding. Indeed, clinicians can adopt a

risk-benefit analysis for patients on a case-by-case basis and consider important factors such as the activity of the disease and the risks on the pregnancy and fetus to offer potential mothers optimal outcomes.

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