Heliyon 9 (2023) e13350

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

# Expert opinion on the pharmacological management of multiple sclerosis in women of childbearing age in Iraq

Hayder K. Hassoun [a,*], Akram Almahdawi [b], Sarwer Jamal Al-Bajalan [c], Nawfal M. Sheaheed [b], Mohammad A.S. Kamil [d], Samer Mohammed Saeed Ridha [e], Mazin M.H. Al-Owath [f], Muataz Fairooz Abd [b], Basim Al-Khammasi [e], Zaki Noah Hasan [g], Anmar Oday Hatem [b], Murad Al-Naqshbandi [h], Peter Rieckmann [i]

[a] *Kufa University, Kufa College of Medicine, Al-Najaf, Iraq*
[b] *Medical City, Baghdad Teaching Hospital, Baghdad, Iraq*
[c] *University of Sulaimani, School of Medicine, Iraq*
[d] *University of Fallujah, College of Medicine, Iraq*
[e] *Neuroscience Teaching Hospital, Baghdad, Iraq*
[f] *Basra College of Medicine, Department of Medicine, Iraq*
[g] *University of Baghdad, Alkindy College of Medicine, Iraq*
[h] *Merck KGaA Middle East Ltd., Merck KGaA, Darmstadt, Germany*
[i] *Bamberg Hospital and University of Erlange, Germany*

ARTICLE INFO

*Keywords:*
Multiple sclerosis
Pregnancy
Women
Iraq
Pharmacological management
Disease-modifying therapies

ABSTRACT

*Background:* Multiple sclerosis (MS) is often diagnosed in women of childbearing age (WCBA), with a mean age of onset of 30 years. Women with MS have long been cautioned to carefully plan their pregnancies and, traditionally, disease-modifying therapies (DMTs) have not been recommended for use in patients engaged in family planning. In 2020, the United States Food and Drug Administration (FDA) approved a label update for interferon beta (IFN ß) by adding new safety data on pregnancy and breastfeeding. Because current management guidelines do not yet reflect the recent label update, a panel of neurology experts from Iraq decided to discuss the potential need for changes in treatment strategies in Iraq.

*Methods:* A panel of experts consisting of 8 neurologists from Iraq and one international neurology expert from Germany convened to develop an expert opinion that would provide practical guidance for the pharmacological management of WCBA with MS in Iraq. They considered the latest label update and relevant published literature, along with local clinical practice and available resources.

*Results:* Interferon and Glatiramer acetate have no evidence of harm during pregnancy. IFN β can be continued safely through pregnancy. Switching treatment during pregnancy is generally not recommended. Short-term intravenous methylprednisolone can be used to treat disabling relapses.

*Conclusion:* Given the complexity of managing MS in pregnant women, it is the opinion of the expert panel that family planning should be discussed early in the disease course, planned pregnancy should be encouraged, and open communication with patient for her treatment

* Corresponding author.
*E-mail address:* drhayder67@hotmail.com (H.K. Hassoun).

https://doi.org/10.1016/j.heliyon.2023.e13350
Received 18 March 2022; Received in revised form 2 January 2023; Accepted 26 January 2023
Available online 31 January 2023
2405-8440/© 2023 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

decisions is paramount. Patients who are engaged in family planning are no longer discouraged from treatment with some of the currently available DMTs.

## 1. Background

In 2015, multiple sclerosis (MS) ranked tenth for prevalence among neurological conditions measured, and the latest epidemiological data from the MS International Federation report 2.8 million cases globally [1]. MS prevalence and incidence vary across different regions of the world. In the Middle East and North Africa (MENA), age-standardized MS prevalence per 100 000 population was 30–59 in 2016, women and men combined [2]. Consistent with the increase in global prevalence of the disease, there is a regional trend toward increased MS prevalence in the MENA region [3]. In 2020, 4355 people live with MS in Iraq, of which 69% are women [1]. Epidemiological data collected via one of the first Middle East MS specialized clinics, the Baghdad MS Clinic at Baghdad University Hospital, reported patient demographic and clinical features similar to those reported in Caucasian populations [4]. This was confirmed by a recent review of the MENACTRIMS (Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis) registry–although compared to Western phenotype, an earlier age at disease onset and a more aggressive clinical course leading to earlier disability were observed in regional patients [3].

Women are disproportionately affected by MS and disability-adjusted life-years (DALYs) are significantly higher in women than in men [2]. The disease is often diagnosed in women of childbearing age (WCBA), with a mean age of onset of 30 years. While MS does not affect a woman's reproductive health, significant consideration is given to potential pregnancy for treatment decisions in WCBA. This is particularly important given the increasing prevalence of pregnancy in women with the neurological condition [5]. This positive outlook from MS patients toward pregnancy is also illustrated by data that show that WCBA make up >40% of all relapsing-remitting MS (RRMS) patients, of which 25% are either pregnant or planning to become pregnant [6].

Women with MS have long been cautioned to carefully plan their pregnancies, as study results collected nearly 20 years ago suggested that women faced a greater risk for relapse in the postpartum period [7]. Traditionally, disease-modifying therapies (DMTs) have not been recommended for use in patients engaged in family planning. Over the years, there have been calls to liberalize these rules [8,9]. Recently, the Food and Drug Administration (FDA) approved a label update for interferon beta (IFN β) by adding new safety data on pregnancy and breastfeeding [10]. The label update was done in accordance with the FDA's Pregnancy and Lactation Labeling Rule and drew from a large amount of data from registries and post-marketing experience, which indicated no increased risk of major congenital anomalies after pre-conception exposure to IFN β, or such exposure during the first trimester of pregnancy [11–15].

Because pregnancy in women with MS can be complex, both from the patient and the provider perspective, and current management guidelines do not yet reflect the recent label update, our panel of experts would like to discuss the potential need for changes in treatment strategies in Iraq, and provide clear, practical, and evidence-based guidance for neurologists who manage WCBA with MS.

## 2. Methods

A panel of experts consisting of 8 neurologists from Iraq and one international neurology expert from Germany met in May 2020. The objective of the meeting was to arrive at an expert opinion that would provide practical guidance for the pharmacological management of WCBA with MS in Iraq based on the latest label update for IFN. The panel of experts discussed and drafted expert opinions on family planning for women with MS during the pre-conception period, pregnancy, and the postpartum period based on the current practices in the region. Three additional neurologists from Iraq reviewed, edited, and commented on the manuscript drafts until a final version was reached and approved by all authors.

## 3. The pre-conception period

### *3.1. Family planning*

It is imperative to include family planning in the treatment plan for WCBA with MS. The plan should address genetic risk, contraception choices, the impact of pregnancy on MS prognosis, the use of DMTs, and assisted reproduction [16]. In Iraq, women with MS are often concerned about the potential impact of the disease on their ability to conceive and the risk to their children. MS is not a genetically inherited disease, but a growing body of evidence suggests that environmental and genetic factors are likely involved [17,18]. Therefore, patients should be counselled on the identified risk or susceptibility genes.

In order to support safe pregnancy, family planning should begin as early as possible in WCBA with MS. This is particularly important in Iraqi culture where pregnancy is highly encouraged in married women. Given the variability in the quality of healthcare across the country, our panel of experts advise that pre-pregnancy counselling should begin at an early stage of the disease. Disease activity and response to treatment should dictate the most appropriate time for pregnancy. Women with persistently high disease activity should generally be advised to delay pregnancy [19]. Pregnancy could be considered in newly diagnosed MS patients with low lesion load (on magnetic resonance imaging) and minor symptoms, even before initiation of DMTs. However, family planning should not delay treatment with DMTs as they have been shown to delay disease progression and reduce long-term disability [20]. Given the unpredictability of the disease course, some neurologists may encourage WCBA newly diagnosed with MS to wait for one year

following the initial diagnosis to assess disease stability and severity prior to becoming pregnant [21].

If family planning is not recommended due to high or unstable disease activity, patients with MS should be counselled on contraception. Oral contraceptives, when taken consistently, are effective and safe. The most effective reversible methods of contraception are long-acting reversible contraceptives such as intrauterine devices because, once in place, they do not require user compliance. Barrier methods, when used consistently and correctly, can also be effective [22]. The panel of experts also recommend the use of dual contraceptives in patients treated with highly teratogenic DMTs.

### 3.2. Pharmacological management

In Iraq, the use of DMTs in the preconception period is generally aligned with current management guidelines and dependent on drug availability: IFN are the first line of treatment, followed by fingolimod or natalizumab. Rituximab is commonly prescribed by neurologists as third-line agent, despite the lack of approved indication for patients with MS. It was recently approved by the Iraq Ministry of Health as salvage therapy for patients with MS in whom second-line therapy cannot be continued [23]. In a recent retrospective cohort study of 74 pregnancies among women treated with rituximab for MS, there was no increase in adverse pregnancy outcomes compared with expected national incidence rates [24]. A systematic review and retrospective case series evaluating the safety of rituximab in MS before and during pregnancy found no major safety signal with rituximab use within six months of conception [25]. However, larger studies are needed to comprehensively assess the safety of periconceptional rituximab and, until these data are available, rituximab before pregnancy should be restricted to women who require highly effective MS treatment.

The panel of experts recommend involving the patient in the selection of DMT. The choice of pharmacological agent should consider the patient's characteristics and comorbidities, the drug safety profile, and the disease severity/activity [19]. Treatment strategies with DMTs for WCBA in Iraq who may be planning a pregnancy are summarized in Fig. 1. To date, only IFN and glatiramer acetate (GA) can be safely continued through pregnancy. It is well known that GA is a valid for treatment during both pregnancy and lactation option, but it is not approved for treatment in Iraq. Discontinuation of natalizumab and fingolimod carry a high risk of

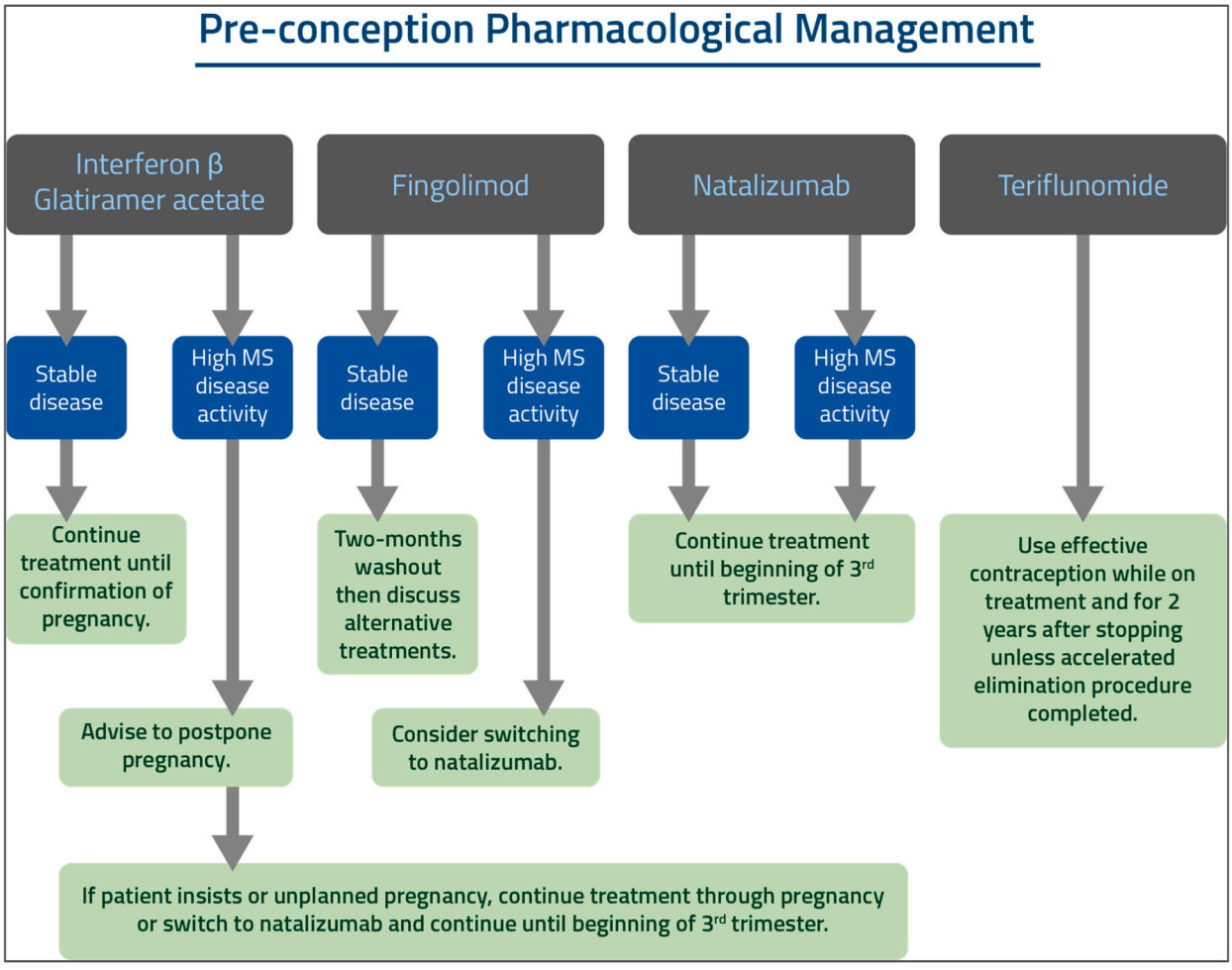


**Fig. 1.** Treatment strategies with DMTs in women planning a pregnancy [31].

rebound (a severe increase in relapse rate) [26,27]. In patients with highly active MS, the panel of experts recommend involving the patient in the decision to either de-escalate treatment to support safe pregnancy or continue treatment with natalizumab to prevent possible rebound.

Women who experience difficulties conceiving may want to consider assisted reproductive technology (ART) or *in vitro* fertilization. Assisted conception can be used in women with MS with long-term disease stability. Some, such as gonadotropin-releasing hormone agonists, are contraindicated [28] as they have been linked to an increased risk for clinical and MRI disease activity. An increase in annualized relapse rate following ART has been reported and may be the result of stress and hormone alterations associated with ART [21,29,30].

The panel of experts identified the following key messages for WCBA with MS who plan on becoming pregnant.

- There is no long-term disability associated with pregnancy.
- Planned over unplanned pregnancy is preferred.
- MS treatment should not be discontinued suddenly without speaking to a physician.
- IFN β can be continued safely through pregnancy.

## 4. Optimizing treatment strategies during pregnancy

Pharmacotherapy in women with MS has been a major issue during pregnancy. Previously, none of the DMTs were recommended for use while pregnant or breastfeeding. Yet, data from the USA and Europe show that approximately half of women with MS who are planning a pregnancy are treated with injectable DMTs [32], with a proportion of pregnancies (both planned and unplanned) resulting in DMT exposure *in utero.* [33] Our recommendations for optimal pharmacological management of women with MS during pregnancy are summarized in Table 1.

DMTs of the IFN class have been available for several years, accumulating a large amount of data on pregnancy exposure. Data from safety registries show no association between IFN β exposure and adverse pregnancy outcomes [11–15,34]. Previous concerns about congenital abnormalities and spontaneous abortion have not been confirmed by these large registry studies. Consequently, several national and international guidelines and recommendations support continuation of IFN throughout pregnancy, as necessary [19,31,35].

Glatiramer acetate is not believed to cross the placenta and there is no evidence from either animal or human studies of an association with negative pregnancy effects [16]. It is licensed for use during pregnancy. However, GA is not currently approved for the treatment of MS in Iraq.

The limited information on the safety of fingolimod during pregnancy means that WCBA with MS should be counselled on using contraception while treated with this DMT [31]. It is known to cross the placenta and requires a 2-month washout period before attempting pregnancy.

While natalizumab is not approved for use during pregnancy, its discontinuation in WCBA who plan to become or are pregnant should be considered carefully given that women eligible for natalizumab usually have rapidly evolving severe MS [31]. Washout recommendations range from 1 to 3 months. Some experts recommend continuing natalizumab at 6 to 8-week extended intervals with the last dose occurring at 30–34 weeks [31,36]. Rebound activity generally occurs 12–16 weeks after discontinuation. Therefore, treatment should be resumed within 8–12 weeks to prevent rebound.

Because it does not carry an indication for MS, there are no safety data available on pregnancy risk and rituximab in women with MS. Our panel of experts do not recommend it in this patient population.

Teriflunomide is teratogenic and carries a strict warning from the FDA and the European Medicines Agency (EMA). Women who wish to conceive should undergo the accelerated elimination procedure or wait for 2 years after stopping the drug [31].

Although clinical relapse is less common during pregnancy, it can occur. The panel of experts emphasize the need to carefully review treatment options with patients, particularly those with high disease activity who might be at greater risk of relapse during pregnancy. Switching treatment during pregnancy is generally not recommended. Short-term intravenous methylprednisolone can be used to treat disabling relapses [31].

Due to the body of evidence indicating an association between lower vitamin D levels and increased risk of MS and disease activity, vitamin D supplementation before, during and after pregnancy is recommended in women with MS [31,37].

**Table 1**
Optimal pharmacological management of women with MS during pregnancy.

| Disease-modifying therapy | Strategy during pregnancy |
|---|---|
| Interferon | No evidence for harm. |
| Glatiramer acetate | No evidence for harm. |
| Fingolimod | Discontinue and allow a 2-month washout period. |
| Natalizumab | Discontinue and allow a 1- to 3-month washout period.<br>Extended interval doses (every 6–8 weeks) can be considered for patients with high disease activity. |
| Rituximab | Not recommended due to lack of safety data. |
| Teriflunomide | Use effective contraception while on treatment and for 2 years after stopping unless the patient undergoes the accelerated elimination procedure. |

MRI is not contraindicated during pregnancy. However, gadolinium contrast media should be avoided when possible [31,38].

## 5. Pharmacotherapy in the postpartum period

The risk of disease relapse is reduced during pregnancy and increases in the postpartum period [39]. As a result, MS treatment should be switched back to the most effective preconception treatment as early as possible. Intravenous methylprednisolone can be used safely for treatment of postpartum relapse, even while breastfeeding [40]. However, there is no evidence to support the use of corticosteroids to prevent postpartum relapse [31].

In Iraq, breastfeeding is recommended for one year following delivery. The effect of exclusive breastfeeding on postpartum MS relapse is controversial. It is unclear whether breastfeeding can suppress MS disease activity [41]. Nevertheless, given the established benefits associated with breastfeeding, the panel of experts encourage exclusive breastfeeding alongside treatment considerations.

If clinically needed, INF β can be considered while breastfeeding. Limited data for lactation suggest that IFN β-1a is not significantly present in breastmilk (0.006% of maternal dose) [42] and does not negatively impact birth characteristics of body weight and length [43]. Furthermore, data from pregnant women with MS treated with GA and IFN β and enrolled into the German Multiple Sclerosis Pregnancy Registry showed that the prevalence of developmental delays in motor skills was in line with that of the general population [43].

Natalizumab crosses into human milk and its prescribing information states that it should be discontinued in women who breastfeed. A panel of experts from the UK indicated that the use of natalizumab should be safe during breastfeeding given its negligible oral bioavailability and subsequent low systemic absorption by the infant [31]. Until more data becomes available, the panel of experts recommend that natalizumab could be used in breastfeeding women with high disease activity, those who relapsed during a previous pregnancy or postpartum period, and those who experienced a relapse in the year prior to becoming pregnant.

Fingolimod and teriflunomide should be avoided by breastfeeding mothers with MS [31].

## 6. Conclusion

This article has summarized the opinion of an expert panel for the pharmacological management of MS in WCBA in Iraq. It is based on international guidelines, the latest medication label updates, as well as available resources and local practice in Iraq. Given the complexity of managing MS in pregnant women, it is the opinion of the expert panel that family planning should be discussed early in the disease course. Planned rather than unplanned pregnancy should be encouraged, and open communication which informs the patient and involves her in treatment decisions is paramount. Patients who are engaged in family planning are no longer discouraged from treatment with some of the currently available DMTs. The panel encourages a systematic, yet personalized treatment approach guided by the most recent safety data.

## Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

## Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Data availability statement

Data included in article/supp. material/referenced in article.

## Declaration of interest's statement

Dr. Nawfal M. Sheaheed received speaker honoraria from Eli Lilly, Bayer, Merck, and Biologix FZCO.

Dr. Murad Al-Naqshbandi is an employee of Merck KGaA Middle East Ltd., an affiliate of Merck KGaA, Darmstadt, Germany.

Prof. Rieckmann has received honoraria for lectures from Allmiral, Apple Healthcare, Bayer, Biogen, Boehringer-Ingelheim, Celgene, Daiichi Sankyo, Genpharm, Medtronic, Merck-Serono, NeuroPlasticity Consulting, Novartis, Pfizer, Roche, Sanofi, Siemens AG, and Teva; research grants from Teva, Oberfranken-Stiftung, German Neurology Foundation, Red Bull, and hpCosmos; and advisory board or steering committee fees from Bayer Biogen Novartis, Merck-Serono, Teva, German Multiple Sclerosis Society, and Canada Drug Review.

## References

[1] The atlas of MS. https://www.atlasofms.org/fact-sheet/iraq.

[2] M.T. Wallin, W.J. Culpepper, E. Nichols, Z.A. Bhutta, T.T. Gebrehiwot, S.I. Hay, et al., Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 18 (3) (2019 Mar 1) 269–285.

[3] B.I. Yamout, W. Assaad, H. Tamim, S. Mrabet, R. Goueider, Epidemiology and phenotypes of multiple sclerosis in the Middle East North Africa (MENA) region, Mult. Sclerosis J. Exp. Transl. Clin 6 (1) (2020 Jan). https://10.1177/2055217319841881.

[4] A. Al-Araji, A.I. Mohammed, Multiple sclerosis in Iraq: does it have the same features encountered in Western countries? J. Neurol. Sci. 234 (1–2) (2005 Jul 15) 67–71.
[5] M.K. Houtchens, N.C. Edwards, G. Schneider, K. Stern, A.L. Phillips, Pregnancy rates and outcomes in women with and without MS in the United States, Neurology 91 (17) (2018 Oct 23) e1559–e1569. https://10.1212/WNL.0000000000006384.
[6] J. White, S. Teoh, J. Vindici, H. Brown, S. Gabriele, The influence of family planning on treatment decisions in relapsing-remitting multiple sclerosis (RRMS) in Europe and the United States. Poster session presented at: clinical aspects of MS - diagnosis and differential diagnosis, Mult. Sclerosis J. 25 (S2) (2019) 357–580.
[7] A. Langer-Gould, J.B. Smith, K.B. Albers, A.H. Xiang, J. Wu, E.H. Kerezsi, et al., Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort, Neurology 94 (18) (2020 May 5) e1939–e1949, https://doi.org/10.1212/WNL.0000000000009374.
[8] P.K. Coyle, Multiple sclerosis and pregnancy prescriptions, Expet Opin. Drug Saf. 13 (12) (2014 Nov 19) 1565–1568. https://10.1517/14740338.2014.973848.
[9] K. Hellwig, Pregnancy in multiple sclerosis, Eur. Neurol. 72 (Suppl. 1) (2014 Sep) 39–42.
[10] IFN β label FDA 2020 update. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103780s5203s5207lbl.pdf.
[11] European IFN-β Pregnancy Registry, Safety monitoring committee, 8th annual report, in: https://www.ema.europa.eu/en/documents/procedural-steps-after/avonex-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf, 2017.
[12] S. Thiel, A. Langer-Gould, M. Rockhoff, A. Haghikia, A. Queisser-Wahrendorf, R. Gold, et al., Interferon-beta exposure during first trimester is safe in women with multiple sclerosis—a prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry, Mult. Sclerosis J. 22 (6) (2016 May) 801–809.
[13] M. Sandberg-Wollheim, E. Alteri, M.S. Moraga, G. Kornmann, Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy, Mult. Sclerosis J. 17 (4) (2011 Apr) 423–430.
[14] EPID multiple sclerosis pregnancy study record. https://clinicaltrials.gov/ct2/show/NCT02749396, 2016.
[15] K. Hellwig, Y. Geissbuehler, M. Sabido, C. Popescu, A. Adamo, J. Klinger, et al., Pregnancy and infant outcomes with interferon beta: data from the European Interferon Beta Pregnancy Registry and population based registries in Finland and Sweden, Mult. Sclerosis and Rel. Disord. 26 (2018 Nov 1) 240.
[16] P.K. Coyle, Management of women with multiple sclerosis through pregnancy and after childbirth, Therap. Adv. Neurol. Disord. 9 (3) (2016 May) 198–210.
[17] H.F. Harbo, R. Gold, M. Tintoré, Sex and gender issues in multiple sclerosis, Therap. Adv. Neurol. Disord. 6 (4) (2013 Jul) 237–248.
[18] C.I. Kucukali, M. Kurtuncu, A. Coban, M. Cebi, E. Tuzun, Epigenetics of multiple sclerosis: an updated review, NeuroMolecular Med. 17 (2) (2015 Jun 1) 83–96.
[19] X. Montalban, R. Gold, A.J. Thompson, S. Otero-Romero, M.P. Amato, D. Chandraratna, et al., ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis, Mult. Sclerosis J. 24 (2) (2018 Feb) 96–120.
[20] G. Comi, M. Radaelli, P.S. Sørensen, Evolving concepts in the treatment of relapsing multiple sclerosis, Lancet 389 (2017 Apr 1) 1347–1356.
[21] M.P. Amato, A. Bertolotto, R. Brunelli, P. Cavalla, B. Goretti, M.G. Marrosu, et al., Management of pregnancy-related issues in multiple sclerosis patients: the need for an interdisciplinary approach, Neurol. Sci. 38 (10) (2017 Oct 1) 1849–1858.
[22] M.K. Houtchens, L.B. Zapata, K.M. Curtis, M.K. Whiteman, Contraception for women with multiple sclerosis: guidance for healthcare providers, Multiple Sclerosis Journal 23 (6) (2017 May) 757–764.
[23] National Board for the Selection of Drugs (NBSD), Iraq Ministry of Health, 2020. Holding no. 1081. 18 January.
[24] J.B. Smith, K. Hellwig, K. Fink, D.J. Lyell, F. Piehl, A. Langer-Gould, Rituximab, MS, and pregnancy, Neurol. Neuroimmunol. Neuroinflamm 7 (4) (2020) e734. https://10.1212/NXI.0000000000000734.
[25] G. Das, V. Damotte, J.M. Gelfand, C. Bevan, B.A.C. Cree, L. Do, et al., Rituximab before and during pregnancy A systematic review, and a case series in MS and, NMOSD Neurol. Neuroimmunol. Neuroinflamm 5 (3) (2018) e453. https://10.1212/NXI.0000000000000453.
[26] E. Portaccio, L. Moiola, V. Martinelli, P. Annovazzi, A. Ghezzi, M. Zaffaroni, et al., Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: II: maternal risks, Neurology 90 (10) (2018) e832–e839. https://10.1212/WNL.0000000000005068.
[27] B. Barry, A.A. Erwin, J. Stevens, C. Tornatore, Fingolimod rebound: a review of the clinical experience and management considerations, Neurol. Therapy 8 (2019 Nov 1) 241–250.
[28] K. Hellwig, J. Correale, Artificial reproductive techniques in multiple sclerosis, Clin. Immunol. 149 (2) (2013 Nov 1) 219–224.
[29] R. Bove, K. Rankin, C. Lin, C. Zhao, J. Correale, L. Michel, et al., Assisted Reproductive Technologies and Relapse Risk: a New Case Series, and Pooled Analysis of Existing Studies, ECTRIMS Online Library, 2017 Oct, p. 352.
[30] K. Rankin, R. Bove, Caring for women with multiple sclerosis across the lifespan, Curr. Neurol. Neurosci. Rep. 18 (7) (2018 Jul 1) 36.
[31] R. Dobson, P. Dassan, M. Roberts, G. Giovannoni, C. Nelson-Piercy, P.A. Brex, UK consensus on pregnancy in multiple sclerosis: association of British Neurologists guidelines, Practical Neurol. 19 (2) (2019 Apr 1) 106–114.
[32] IPSOS, MS Monitor Q2, Data on file with Merck, 2018.
[33] A. Smith, Cohen Ontaneda, Rensel, Unplanned Pregnancy Risk in a United States Multiple Sclerosis Patient Cohort, ECTRIMS Online Library, 2017 Oct, p. 358.
[34] A.L. Nguyen, E.K. Havrdova, D. Horakova, G. Izquierdo, T. Kalincik, A. van der Walt, et al., Incidence of pregnancy and disease-modifying therapy exposure trends in women with multiple sclerosis: a contemporary cohort study, Mult. Sclerosis Rel. Disord. 28 (2019 Feb 1) 235–243.
[35] J. Thoene, S. Thiel, R. Gold, K. Hellwig, Treatment of multiple sclerosis during pregnancy–safety considerations, Expet Opin. Drug Saf. 16 (5) (2017 May 4) 523–534.
[36] A.M. Langer-Gould, Pregnancy and family planning in multiple sclerosis, Continuum 25 (3) (2019 Jun 1) 773–792.
[37] M.B. Sintzel, M. Rametta, A.T. Reder, Vitamin D and multiple sclerosis: a comprehensive review, Neurology and Therapy 7 (1) (2018 Jun 1) 59–85.
[38] J.G. Ray, M.J. Vermeulen, A. Bharatha, W.J. Montanera, A.L. Park, Association between MRI exposure during pregnancy and fetal and childhood outcomes, JAMA 316 (9) (2016 Sep 6) 952–961.
[39] A. Rae-Grant, G.S. Day, R.A. Marrie, A. Rabinstein, B.A.C. Cree, G.S. Gronseth, et al., Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology, Neurology 90 (17) (2018 Apr) 777–788. https://10.1212/WNL.0000000000005347AAN.
[40] C. Boz, M. Terzi, S. Zengin Karahan, S. Sen, Y. Sarac, M. Emrah Mavis, Safety of IV pulse methylprednisolone therapy during breastfeeding in patients with multiple sclerosis, Mult. Sclerosis J. 24 (9) (2018 Aug) 1205–1211.
[41] K. Hellwig, M. Rockhoff, S. Herbstritt, N. Borisow, A. Haghikia, B. Elias-Hamp, et al., Exclusive breastfeeding and the effect on postpartum multiple sclerosis relapses, JAMA Neurol. 72 (10) (2015 Oct 1) 1132–1138.
[42] T.W. Hale, A.A. Siddiqui, T.E. Baker, Transfer of interferon β-1a into human breastmilk, Breastfeed. Med. 7 (2) (2012 Apr 1) 123–125.
[43] A.I. Ciplea, A. Stahl, S. Thiel, R. Gold, K. Hellwig, Interferon-β/glatiramer acetate treatment during lactation in women with multiple sclerosis, in: Poster Presented at: 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS), Berlin, Germany, 2018 Oct 10-12.