



Pregnancy outcome in patients with multiple sclerosis: A retrospective study from single center in Benghazi, Libya

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Anwaar Mukhtar Bennour^{1,2}, Magda Elshukri^{1,2}, Naziha Amer¹, Heba El-Zawawi^{1,2}, Abdulhameed Zawawi^{1,2}

¹ Department of Internal Medicine, Neurology Unit, Multiple Sclerosis Clinic, Benghazi Medical Center, Benghazi, Libya

² Department of Medicine, School of Medicine, University of Benghazi, Benghazi, Libya

Keywords

Pregnancy; Multiple Sclerosis; Postpartum Period; Recurrence; Breast Feeding; Libya

Abstract

Background: Misconceptions about multiple sclerosis (MS), pregnancy, and disease-modifying therapies (DMTs) are common, often driven by fears that DMTs pose risks to the fetus or that pregnancy will exacerbate the disease. This study aimed to evaluate and document local clinical practices and decision-making processes in the management of women with MS regarding DMT use during pregnancy.

Methods: A retrospective review was conducted at the MS Clinic of Benghazi Medical Center, Benghazi, Libya, from January 1, 2016 to December 31, 2019. Medical records of women meeting the 2017 McDonald's criteria for MS diagnosis were analyzed. Data collected included demographic and clinical variables, pregnancy outcomes, DMT use, and postpartum care. Statistical analysis was performed using SPSS software.

Results: Thirty-six women (61 pregnancies) were

included. The median age was 36 years (range: 24-56). Unplanned pregnancies occurred in 24/36 women, 32/61 pregnancies (52%). Only five women continued DMTs during pregnancy. Uncomplicated pregnancies occurred in 30/36 women (83%), while postpartum relapses were reported in 12 women (33%), 11 with unplanned pregnancies. The median time to DMT resumption postpartum was 4 months. Breastfeeding was practiced for a median duration of 4 months. Preconception magnetic resonance imaging (MRI) was performed in 6 women (16.6%).

Conclusion: This study provides valuable insights into the management of MS during pregnancy in Libya. While the sample size is small, the findings underscore the importance of standardized guidelines for DMT use, pregnancy planning, and postpartum care. Future studies with larger cohorts and broader DMT options are needed.

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by demyelination of the central nervous system (CNS). It predominantly affects women, with a female-to-male ratio of 3:1.^{1,2} MS is often diagnosed during the reproductive years, raising concerns about its management during pregnancy and postpartum.

Pregnancy in women with MS presents unique challenges; deferring treatment until the family is completed can lead to irreversible disability in the long term.^{3,4} The PRegnancy in Multiple Sclerosis (PRIMS) project suggested that the relapse rate was decreased during 9 months of pregnancy, and increased in the first three months of postpartum period.⁵ In addition, having MS should not influence delivery methods, and mode of delivery should be decided based on obstetrical causes.³ Furthermore, it has been reported that exclusive breast feeding is protective against relapse in MS.⁶

The disease-modifying therapies (DMTs) approved for the treatment of MS include several forms of injectable and oral forms as well as infusion therapy with monoclonal antibody. The use of DMTs during pregnancy or breast feeding frequently gives rise to concerns regarding potential risks to the fetus. Consequently, it is sensible that most doctors generally advise women with MS to discontinue use of DMTs before conception due to fear of teratogenicity and limited information about safety of these drugs in the previous years.⁷ However, data from large systematic review, registry-based cohorts, and worldwide drug experience databases suggested no adverse effects of interferon- β (IFN- β) on pregnancy outcomes.⁷⁻¹¹ Results from these studies showed that pregnancies exposed to IFN- β were found to be associated with reduced mean birth weight and birth length and preterm birth (< 37 weeks); however, there was no increased risk of serious pregnancy complications of spontaneous abortion, cesarean delivery, or birth weight < 2.5 kg.

During the time of conducting this study, which coincided with post-war years in Libya, IFN- β was the most commonly available therapeutic option for patients with MS registered in our center. This limited the prescription options of DMTs to our patients to injectable IFN- β . According to data from MS registry in our center, 94% of the patients had relapsing remitting MS (RRMS) and 82% had mild disease severity with mean Expanded Disability Status Scale (EDSS) score of 1.5, making IFN- β a suitable treatment for them.¹²

Few studies about MS were conducted in Benghazi, Libya, over decades.¹²⁻¹⁴ The prevalence rate of MS in Benghazi was 4/100000 in the year 1984¹³ reaching to 14.8/100000 in the years 2010-2017.¹⁴ These studies addressed the prevalence rate, demographic characteristics, and types of MS in Benghazi, but no data were available with regard to MS management protocol during pregnancy and family planning. Therefore, a high level of interest surrounding the prescription of DMTs in pregnancy will expand the limited applicability of knowledge and experience of our local practicing neurologists when managing patients with MS of childbearing age.

The aim of the present study was to evaluate and document local clinical practices and decision-making processes in the management of women with MS regarding DMT use during pregnancy. This is towards making better progress and optimizing the care of women with MS with childbearing potential.

Materials and Methods

Study design and setting: This is a retrospective study carried out in MS clinic at Benghazi Medical Center (BMC). The MS clinic at BMC was created in the year 2016. BMC is the only public tertiary center to which all cases of MS are referred. In addition to the main town Benghazi, it includes the referred cases from hospitals in the eastern parts of Libya. The authors thoroughly reviewed the documented medical records of the patients who were referred to and registered in the MS clinic at BMC from the period January 1, 2016 till December 31, 2019. The description of the study population and design was reported previously by Bennour et al.¹⁵

Inclusion criteria were: diagnosis of MS based on the 2017 McDonald's criteria, women who experienced MS symptoms or diagnosis during pregnancy, after abortion, or postpartum, and women who conceived after an MS diagnosis. Exclusion criteria included: patients not meeting the 2017 McDonald's criteria, pregnancies occurring before/after the study period, and patients managed outside the MS clinic.

Data collection: From medical records of eligible patients, we thoroughly reviewed the documented follow-up notes of the local expert neurologist and collected demographic and clinical variables (Table 1). Variables included age, types of MS, duration of MS diagnosis, and the EDSS score.

Table 1. Clinical characteristics of the study population

| Variable | Total number (36 women) |
|---|-------------------------|
| Age at MS onset (year) | 36 (24-56) |
| Duration of MS (year) | 7 (1-21) |
| Duration between MS diagnosis and conception (year) | 2 (1-12) |
| EDSS score | 1.0 (0.0-6.0) |
| MS types | |
| RRMS | 35 (97) |
| SPMS | 1 (3) |
| Pregnancy outcomes | |
| Uncomplicated pregnancy | 30 (83) |
| Miscarriage | 6 (17) |
| Postpartum relapse | 12 (33) |
| Delivery outcomes | |
| Vaginal delivery | 23/30* |
| Caesarean section | 7/30* |
| Resumption of DMT (month) | 4 |
| Duration of breast feeding (month) | 4 |

Values are expressed as median and range (numerical variables) and number and percentage (categorical variables).

*Women who completed their pregnancies

MS: Multiple sclerosis; DMT: Disease-modifying therapy; EDSS: Expanded Disability Status Scale; RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

The authors focused on the action plan taken regarding DMTs during or before pregnancy occurrence which included discontinuation versus maintaining DMTs when pregnancy was confirmed. Also reviewed were the proportions of cases with planned and unplanned pregnancies, the disease course during pregnancy and after delivery, delivery methods, time of resumption of DMTs, and breast feeding as well as whether patients had had magnetic resonance imaging (MRI) before conception.

The statistical tests used were descriptive statistics where frequencies of variables were expressed as median and ranges for numerical variables or numbers and percentages for categorical variables. Normally distributed numerical variables (age, duration of MS diagnosis, time to conceive after MS diagnosis, number of pregnancies, EDSS score, time to resume DMT, duration of breast feeding) were assessed using the Kolmogorov-Smirnov Z test. Differences between groups were assessed using independent samples t-test or chi-square test as appropriate. The effect sizes were calculated using Cohen's d for independent samples t-test and Cohen's Omega for chi-square test. All statistical analyses were performed using the SPSS software (version 26, IBM Corporation, Armonk, NY, USA).

Ethical considerations: Although our study was retrospective and involved analysis of existing data, approval from the Ethics Research Board at

BMC was obtained before commencing the study to ensure adherence to ethical standards and regulations. All patients gave a verbal consent to participate in the study. To ensure confidentiality, data were anonymized by encrypting identifiable information such as names, addresses, and national numbers.

Results

Study population: The total number of patients with MS registered in the clinic during the study period was 360 patients; 169 (72%) were women, 40 (24%) were married. Thirty six (36/169, 21%) women (61 pregnancies) were documented. The median age was 36 (24-56) years. Thirty five (97%) had RRMS, with a median EDSS score of 1.0 (0.0-6.0). The median duration of MS diagnosis was 7 (1-21) years, and the median duration lapsed between diagnosis of MS and pregnancy was 2 (1-12) years.

Pregnancy outcomes: Unplanned pregnancies were documented in 24/36 women, 32/61 pregnancies (52%). Uncomplicated pregnancies occurred in 30/36 women (83%). Miscarriage occurred in six (17%) women.

Planned versus unplanned pregnancies (Table 2): A statistically significant difference was observed in the cessation versus continuation of DMTs between women with planned and unplanned pregnancies (12 vs. 0 and 19 vs. 5, respectively, $P < 0.001$, effect size = 0.13).

Table 2. Differences in variables between planned and unplanned pregnancies in the cohort study of 36 women with multiple sclerosis (MS)

| Variable | Planned pregnancy (n = 12, 33%) | Unplanned pregnancy (n = 24, 67%) | P | Effect size |
|-------------------------------------|------------------------------------|--------------------------------------|---------|-------------|
| Age (year) | 36 (24-48) | 37 (27-56) | 0.750 | -0.13 |
| Duration of MS (year) | 9 (1-21) | 8 (2-21) | 0.560 | 0.20 |
| Time to conceive after MS diagnosis | 4.2 (1.0-12.0) | 2.8 (1.0-12.0) | 0.250 | 0.34 |
| EDSS score | 1.3 (0.0-6.0) | 1.5 (0.0-5.0) | 0.800 | -0.09 |
| Use of DMTs | | | < 0.001 | 0.13 |
| Cessation | 12 (100) | 19 (79) | | |
| Continuation | 0 (0) | 5 (21) | | |
| MS categories | | | 0.310 | 0.04 |
| RRMS | 11 (92) | 24 (100) | | |
| SPMS | 1 (8) | 0 (0) | | |
| Pregnancy course | | | 0.050 | 0.08 |
| Uncomplicated | 11 (92) | 19 (79) | | |
| Miscarriage | 1 (8) | 5 (21) | | |
| Postpartum course | | | 0.026 | 0.09 |
| Relapse | 1 (8) | 11 (46) | | |
| No relapse | 11 (92) | 13 (54) | | |

Values are expressed as median and range (numerical variables) and number (percentage) for categorical variables.

MS: Multiple sclerosis; DMTs: Disease-modifying therapies; EDSS: Expanded Disability Status Scale; RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

However, no significant difference was found in the type of MS [RRMS vs. secondary progressive MS (SPMS)] between the two groups (11 vs. 1 and 24 vs. 0, $P = 0.31$). Additionally, there were no significant differences between women with planned and unplanned pregnancies in terms of age, duration of MS diagnosis, time to conception after diagnosis, EDSS score, or duration of DMT resumption.

DMTs: The only feasible treatment was injectable IFN- β . Only five women (all with unplanned pregnancy) decided to continue their DMT during pregnancy. On the other hand, three women decided to defer their DMTs till they had completed their family. The remaining women stopped their DMTs when pregnancy was confirmed (in cases of unplanned pregnancies, and 2 months prior to conception when pregnancies were planned).

Delivery outcomes among women who completed their pregnancies ($n = 30$): Normal vaginal delivery occurred in 23 women (77%), while 7 women (23%) underwent caesarean section. Among women with unplanned pregnancy, only one patient gave birth to an abnormal child.

Postpartum: Postpartum relapse was reported in 12 women, 11 among women with unplanned pregnancies (Table 2). The median duration to resume DMTs was four (0-6) months and the median breast feeding duration was four months.

Preconception MRI: Six (21%) women had performed MRI of the brain prior to conception.

Discussion

The diagnosis of MS and use of DMTs may affect marital relationships, particularly in societies of Arab world, where fertility and childbearing are highly valued. The treatment of women with MS in the childbearing age is challenging and the prescription decision for DMTs during pregnancy is an area of active research.¹⁶ It should be emphasized that glatiramer acetate (GA) is the safest DMT used during pregnancy;¹⁷⁻²⁰ however, it is not offered for the majority of the countries in the Middle East including Libya.

At the time of conducting the study, the availability of DMTs for all patients with MS in our setting was limited to IFN- β as first-line therapy. The shortage of drugs was partly related to the fact that in 2016, the Libyan drug stores were just recovering after the Libyan war. Moreover, the MS clinic at BMC was just established for patients' registration in the year 2016.

In the present study, the authors explored the decisions taken in every day clinical practice regarding DMTs and pregnancy in the MS clinic in our hospital. It was found that nearly half of the reported pregnancies were unplanned, which is expected, as half of the pregnancies worldwide are unplanned.²¹ In the majority of our patients who wished to start pregnancy or who had an

unplanned pregnancy, the treatment was discontinued either 2-3 months prior to conception or once pregnancy was confirmed. The action of either stopping or delaying treatment in women planning pregnancy was previously reported in other studies.²²⁻²⁵

Withdrawal of DMTs in pregnancy or deferring treatment was an issue to consider because of risk of increasing diseases activity. It has been shown that discontinuation of DMTs before becoming pregnant is associated with increased relapse rate during pregnancy and after delivery,^{26,27} especially in patients treated with high efficacy therapy such as natalizumab and fingolimod.²⁸

All of our patients were treated with IFN- β and none were using high efficacy therapy; therefore, further broader studies of different types of DMTs during pregnancy are warranted. Data from United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) indicate that treatment with IFN- β has no risk of birth defect, and contraception is not indicated.²⁹ The recommendations from experts in management of MS during pregnancy are: initiating DMTs at diagnosis of MS and establishing clinical stability for ≥ 1 year before attempting to conceive.³⁰ With growing recognition of the importance of early intervention, a new era has begun regarding the use of DMTs in patients with MS during pregnancy and family planning. This shift is supported by consensus guidelines from the United Kingdom (UK)³ and data from the Persian Gulf.^{31,32} The UK consensus specifically recommends continuing the use of GA, interferons (IFNs), and dimethyl fumarate (DMF) during pregnancy. Natalizumab can also be continued till the end of the second trimester due to high risk of disease reactivation if it is stopped.³³ Based on these recommendations, reluctance in the decision of prescribing DMTs in pregnancy should be eliminated.

Only a few patients had an abortion or relapse during pregnancy, and in the majority, the pregnancy course and outcome were uncomplicated. The findings align with global data showing a reduced relapse rate during pregnancy.³⁴

Among patients who developed postpartum relapse, the reasons were either those patients had more than one relapse in the pre-pregnancy year or had deferred treatment because they wished to complete their family or had discontinued their treatment for a period of more than one year leaving the disease untreated. These explanations

are withdrawn based on data from the MSBase registry which show that higher pre-conception annual relapse rate predicts early postpartum relapse and use of DMTs in the two years preconception has an independent protective effect.³⁵ Data about the frequency and severity of relapses before pregnancy, which could impact pregnancy outcomes, were not feasible to retrieve from our dataset; however, the postpartum relapse in our patients could be related to limited treatment option with IFN- β .

Fortunately, in the whole register, we did not have many patients with high disease activity. In dealing with such cases in future, we will consider high efficacy therapy with induction therapy to control disease activity before conception occurs.

In the present study, there were no congenital malformations reported in our patients, and the only abnormal child was born with cerebral palsy (CP), a condition that cannot solely be due to exposure to IFN. Furthermore, choosing caesarean section as a mode of delivery in those women whose delivery was not vaginal, was related to reasons other than MS, and these included big size baby, patient's choice, breech presentation of the baby, uncontrolled diabetes, fetal distress, and a previous uterine scar. Therefore, women with MS should be carefully counselled regarding the facts that MS has no impact on their ability to conceive, carry on a normal pregnancy, and give birth to a normal healthy baby.

As breast feeding is found to be protective against MS reactivation,^{6,36} and IFN is not excreted in breast milk,³⁷ our patients were encouraged to breastfeed unless the mother was not willing to do so. This is emphasized by the EMA and the US FDA safety data on the use of IFN- β during lactation.³⁸

The assessment of preconception disease activity using MRI was feasible to six women only, reflecting logistical challenges. As MRI can capture asymptomatic lesions, it is important to ensure the needs for this subset of patients to have a preconception as well as a postpartum surveillance MRI. In previous reports, MRI is not contraindicated during pregnancy, but gadolinium use is associated with risks to the fetus.^{39,40}

Although cannot be generalized, the results can be utilized to offer a local guide to DMTs prescription during pregnancy in a resource limited setting. Future studies with larger cohorts and broader DMT options are needed to refine these recommendations:

Family planning counseling: Discuss family planning early in MS management,

DMT use during pregnancy: Consider IFN- β or natalizumab for women with high disease activity,

Delivery mode: Base decisions on obstetric indications,

Breastfeeding: Encourage breastfeeding,

Preconception MRI: Perform MRI before conception to assess disease activity.

Limitations: The study has several limitations that should be acknowledged. First, its generalizability may be constrained due to the single-center design and relatively small sample size. The MS clinic at BMC serves as the sole authorized referral center for all patients with MS in Benghazi and the eastern regions of Libya, which inherently restricted the study to a single-center framework. Second point is the small sample size which can be attributed to two main factors: the short duration of the study period and the early stage of the MS clinic establishment at BMC in 2016. At that time, patient registration had only recently begun, resulting in a limited number of cases. Additionally, population displacement caused by the ongoing conflict in Libya during that

period may have further contributed to the reduced patient numbers. These factors collectively limit the broader applicability of the study findings.

Conclusion

This study provides valuable insights into the management of MS during pregnancy in Libya. While the sample size is small, the findings underscore the importance of standardized guidelines for DMT use, pregnancy planning, and postpartum care. Future studies with larger cohorts and broader DMT options are needed.

Conflict of Interests

The authors declare no conflict of interest in this study.

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