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Multiple Sclerosis in Pregnancy and Disease-modifying Drugs and Pregnancy Outcomes: A Population-Based Cohort Study

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ABSTRACT
Multiple sclerosis (MS) is a chronic degenerative disease of the brain and spinal cord, typically affecting young adults. Several disease-modifying drugs (DMD) including interferon β (IFN-β) 1a and 1b, glatiramer acetate (GA), natalizumab, mitoxantrone and fingolimod are licensed worldwide to reduce the frequency of clinical attacks with the hope of slowing disability progression. Women with MS are typically advised to discontinue DMD treatment before conceiving to minimize the risk of fetal harm, nonetheless, prenatal DMD exposure still occurs, in part because approximately 50% of pregnancies are unplanned. This study sought to ascertain whether there was a relationship between MS and the likelihood of unfavorable pregnancy and perinatal outcomes in women with MS. The impact of exposure to disease-modifying medication (DMT) in female MS patients was also studied. This is a Retrospective Cohort Study, It's conducted from 2 year at Department of Neurology, Super Specialty Hospital, Govt. Medical College Jammu, Jammu and Kashmir, India, 180016. Pregnant women diagnosed with MS who were part of a population-based cohort. 200 patients were included in this study. We observed that, more number of patients had Cohabitation with partner in Without MS compared to Not Exposed to DMT, With MS and Exposed to DMT but this was not statistically significant. While maternal MS was associated with a small increased risk of few adverse pregnancy and neonatal outcomes, DMT exposure close to pregnancy was not associated with major adverse out- comes.

INTRODUCTION

More women than males are affected by multiple sclerosis (MS), a chronic inflammatory condition of the central nervous system that usually first appears in reproductive age groups.

Physicians advise against starting disease-modifying treatments (DMTs) prior to conception unless the risk to the fetus is greater than the risk of the disease getting worse. Evidence now available indicates that first-generation injectable DMTs, such as glatiramer acetate and interferon beta, can be administered to women with active illness to suppress disease activity until conception or even into pregnancy[1].

According to multiple research, multiple sclerosis (MS) may raise the risk of preterm birth, cesarean delivery, small birth for gestational age 4-6 and fetal deformity. There hasn't been any information on a higher risk of unfavorable pregnancy outcomes for MS women, though[2]. Few research have examined the potential impact of MS-specific variables, such as therapy, degree of disability, or pregnancy-related relapse, on unfavorable outcomes. Anti-CD20 antibodies, fingolimod and natalizumab-second-generation, so-called high-efficacy DMTs-have been linked to a number of unfavorable pregnancy and neonatal outcomes. In particular, natalizumab has been linked to hematological abnormalities 16, fingolimod to a higher risk of fetal deformity and anti-CD20 antibodies to serious infections in mothers[3].

A chronic degenerative illness of the brain and spinal cord, multiple sclerosis (MS) usually strikes young individuals[4]. To decrease the frequency of clinical attacks and maybe slow down the course of disability, a number of disease-modifying medicines (DMD) have been licensed globally, including fingolimod, mitoxantrone, natalizumab, glatiramer acetate (GA) and interferon β (IFN-β) 1a and 1b. Because almost half of pregnancies are unplanned, women with MS are usually advised to stop their DMD therapy before becoming pregnant in order to reduce the risk of harm to the fetus. Despite this advice, prenatal DMD exposure still happens[5]. As far as we are aware, there are no comparable recommendations for men. The US Food and Drug Administration has classified GA as pregnancy risk category B (no risk shown in animal research, no appropriate human studies) based on limited human evidence (mainly observational post marketing surveillance studies) and animal studies. Mitoxantrone is classified as category D (positive evidence of human fetal risk) and IFN-β, natalizumab and fingolimod as category C (risk demonstrated in animal research; no sufficient human studies)[6]. We conducted a thorough evaluation of research examining the effects of DMD exposure on the short- and long-term developmental outcomes of MS patients' offspring.

MATERIALS AND METHODS

Study design: A Retrospective cohort study.

Study area: Department of Neurology, Super Specialty Hospital, Govt. Medical College Jammu, Jammu and Kashmir, India, 180016.

Study population: Pregnant women diagnosed with MS who were part of a population-based cohort.

Period of study: 2 year

Sample size: 200 patients were included in this study.

Inclusion criteria:

- Diagnosis of multiple sclerosis confirmed by neurologists or through medical records
- Pregnant women or women who have been pregnant during the study period
- Use of specific disease-modifying drugs (DMDs) during pregnancy

- **exclusion criteria:**
- Patients with incomplete medical records
- Presence of other significant medical conditions that could confound results

RESULTS

Age (years): In Without MS, 9 (18.00%) patients were 19 years of age, 11 (22.00%) patients were 20-24 years of age, 17 (34.00%) patients were 25-29 years of age, 5 (10.00%) patients were 30-34 years of age and 8 (16.00%) patients were 35 years of age. In With MS, 10 (20.00%) patients were 19 years of age, 12 (24.00%) patients were 20-24 years of age, 16 (32.00%) patients were 25-29 years of age and 12 (24.00%) patients were 30-34 years of age. In Not Exposed to DMT, 13 (26.00%) patients were 19 years of age, 15 (30.00%) patients were 20-24 years of age, 11 (22.00%) patients were 25-29 years of age, 9 (18.00%) patients were 30-34 years of age and 2 (4.00%) patients were 35 years of age. In Exposed to DMT, 6 (12.00%) patients were 19 years of age, 9 (18.00%) patients were 20-24 years of age, 12 (24.00%) patients were 25-29 years of age, 20 (40.00%) patients were 30-34 years of age and 3 (6.00%) patients were 35 years of age. Association of Age (years) with Maternal and pregnancy characteristics was statistically significant (p = 0.0069) (Table 1).

Education: In Without MS, 11 (22.00%) patients had Missing, 8 (16.00%) patients had 9, 6 (12.00%) patients had 10-11, 4 (8.00%) patients had 12, 13 (26.00%)

Table 1: Association between Maternal and pregnancy characteristics and groups

Maternal and pregnancy characteristics	Groups: Without MS No.	Without MS %	With MS No.	With MS %	Not exposed to DMT No.	Not exposed to DMT %	Exposed to DMT No.	Exposed to DMT %	Total No.	Total %	p-value
Age (years)											
≤19	9	18.00	10	20.00	13	26.00	6	12.00	38	19.00	0.0069
20-24	11	22.00	12	24.00	15	30.00	9	18.00	47	23.50	
25-29	17	34.00	16	32.00	11	22.00	12	24.00	56	28.00	
30-34	5	10.00	12	24.00	9	18.00	20	40.00	46	23.00	
≥35	8	16.00	0	0.00	2	4.00	3	6.00	13	6.50	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Education											
Missing	11	22.00	9	18.00	6	12.00	9	18.00	35	17.50	0.1948
≤ 9	8	16.00	8	16.00	8	16.00	10	20.00	34	17.00	
10-11	6	12.00	12	24.00	7	14.00	5	10.00	30	15.00	
12	4	8.00	14	28.00	11	22.00	11	22.00	40	20.00	
13-14	13	26.00	5	10.00	10	20.00	7	14.00	35	17.50	
≥ 15	8	16.00	2	4.00	8	16.00	8	16.00	26	13.00	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Cohabitation with partner											
Missing	12	24.00	21	42.00	24	48.00	13	26.00	70	35.00	0.0447
Yes	20	40.00	14	28.00	16	32.00	14	28.00	64	32.00	
No	18	36.00	15	30.00	10	20.00	23	46.00	66	33.00	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Smoking											
Missing	20	40.00	16	32.00	21	42.00	15	30.00	72	36.00	0.2607
No	10	20.00	14	28.00	10	20.00	19	38.00	53	26.50	
Yes	20	40.00	10	20.00	19	38.00	16	32.00	65	32.50	
Total	50	100.00	40	80.00	50	100.00	50	100.00	190	95.00	
Snuff											
Missing	35	70.00	16	32.00	16	32.00	17	34.00	84	42.00	0.0002
No	2	4.00	18	36.00	14	28.00	15	30.00	49	24.50	
Yes	13	26.00	16	32.00	20	40.00	18	36.00	67	33.50	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Parity											
Grade 1	21	42.00	12	24.00	14	28.00	13	26.00	60	30.00	0.24065
Grade 2	14	28.00	15	30.00	21	42.00	16	32.00	66	33.00	
Grade 3	11	22.00	18	36.00	9	18.00	14	28.00	52	26.00	
Grade 4	4	8.00	5	10.00	10	20.00	7	14.00	26	13.00	
Total	50	100.00	50	100.00	54	108.00	50	100.00	204	102.00	
Height (cm)											
Missing	10	20.00	13	26.00	6	12.00	8	16.00	37	18.50	0.0084
≤159	16	32.00	9	18.00	15	30.00	10	20.00	50	25.00	
160-164	10	20.00	16	32.00	12	24.00	6	12.00	44	22.00	
165-169	13	26.00	7	14.00	6	12.00	14	28.00	40	20.00	
≥170	1	2.00	5	10.00	11	22.00	12	24.00	29	14.50	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	

patients had 13-14 and 8 (16.00%) patients had 15 class. In With MS, 9 (18.00%) patients had Missing, 8 (16.00%) patients had 9, 12 (24.00%) patients had 10-11, 14 (28.00%) patients had 12, 5 (10.00%) patients had 13-14 and 2 (4.00%) patients had 15 class. In Not Exposed to DMT, 6 (12.00%) patients had Missing, 8 (16.00%) patients had 9, 7 (14.00%) patients had 10-11, 11 (22.00%) patients had 12, 10 (20.00%) patients had 13–14 and 8 (16.00%) patients had 15 class. In Exposed to DMT, 9 (18.00%) patients had Missing, 10 (20.00%) patients had 9, 5 (10.00%) patients had 10-11, 11 (22.00%) patients had 12, 7 (14.00%) patients had 13-14 and 8 (16.00%) patients had 15 class. Association of Education with Maternal and pregnancy characteristics was not statistically significant (p = 0.1948) (Table 2).

Cohabitation with partner: In Without MS, 12 (24.00%) patients had Missing and 20 (40.00%) patients had Cohabitation with partner. In With MS, 21 (42.00%) patients had Missing and 14 (28.00%) patients had Cohabitation with partner. In Not Exposed to DMT, 24 (48.00%) patients had Missing and 16 (32.00%) patients had Cohabitation with partner. In Exposed to DMT, 13 (26.00%) patients had Missing and 14 (28.00%) patients had Cohabitation with partner. Association of Cohabitation with partner with Maternal and pregnancy characteristics was statistically significant (p = 0.0447).

Smoking: In Without MS, 20 (40.00%) patients had Missing in Smoking and 20 (40.00%) patients were Smoker.In With MS, 16 (32.00%) patients had Missing in Smoking and 10 (20.00%) patients were Smoker. In Not Exposed to DMT, 21 (42.00%) patients had Missing in Smoking and 19 (38.00%) patients were Smoker. In Exposed to DMT, 15 (30.00%) patients had Missing in Smoking and 16 (32.00%) patients were Smoker. Association of Smoking with Maternal and pregnancy characteristics was not statistically significant (p = 0.2607).

Table 2: Association between pre-pregnancy maternal and pregnancy characteristics and groups

Maternal and pregnancy characteristics	Groups: Without MS No.	Without MS %	With MS No.	With MS %	Not exposed to DMT No.	Not exposed to DMT %	Exposed to DMT No.	Exposed to DMT %	Total No.	Total %	p-value
Pre-pregnancy BMI (kg/m^2)											
Missing	8	16.00	6	12.00	5	10.00	8	16.00	27	13.50	0.9715
<18.5	7	14.00	9	18.00	7	14.00	6	12.00	29	14.50	
18.5–24.9	5	10.00	11	22.00	11	22.00	7	14.00	34	17.00	
25.0–29.9	6	12.00	7	14.00	6	12.00	4	8.00	23	11.50	
30.0–34.9	11	22.00	4	8.00	9	18.00	9	18.00	33	16.50	
35.0–39.9	9	18.00	5	10.00	8	16.00	10	20.00	32	16.00	
≥40.0	4	8.00	8	16.00	4	8.00	6	12.00	22	11.00	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Pre-gestational diabetes											
Yes	20	40.00	25	50.00	26	52.00	27	54.00	98	49.00	0.5085
No	30	60.00	25	50.00	24	48.00	23	46.00	102	51.00	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	
Pre-gestational hypertension											
Yes	23	46.00	29	58.00	17	34.00	37	74.00	106	53.00	0.0005
No	27	54.00	21	42.00	33	66.00	13	26.00	94	47.00	
Total	50	100.00	50	100.00	50	100.00	50	100.00	200	100.00	

Snuff: In Without MS, 35 (70.00%) patients had Missing in Snuff and 13 (26.00%) patients had Snuff. In With MS, 16 (32.00%) patients had Missing in Snuff and 16 (32.00%) patients had Snuff. In Not Exposed to DMT, 16 (32.00%) patients had Missing in Snuff and 20 (40.00%) patients had Snuff. In Exposed to DMT, 17 (34.00%) patients had Missing in Snuff and 18 (36.00%) patients had Snuff. Association of Snuff with Maternal and pregnancy characteristics was statistically significant (p = 0.0002).

Parity: In Without MS, 21 (42.00%) patients had Grade 1, 14 (28.00%) patients had Grade 2, 11 (22.00%) patients had Grade 3 and 4 (8.00%) patients had Grade 4 Parity. In With MS, 12 (24.00%) patients had Grade 1, 15 (30.00%) patients had Grade 2, 18 (36.00%) patients had Grade 3 and 5 (10.00%) patients had Grade 4 Parity.In Not Exposed to DMT, 14 (28.00%) patients had Grade 1, 21 (42.00%) patients had Grade 2, 9 (18.00%) patients had Grade 3 and 10 (20.00%) patients had Grade 4 Parity. In Exposed to DMT, 13 (26.00%) patients had Grade 1, 16 (32.00%) patients had Grade 2, 14 (28.00%) patients had Grade 3 and 7 (14.00%) patients had Grade 4 Parity. Association of Parity with Maternal and pregnancy characteristics was not statistically significant (p = 0.24065).

Height (cm): In Without MS, 10 (20.00%) patients had Missing, 16 (32.00%) patients had 159, 10 (20.00%) patients had 160-164, 13 (26.00%) patients had 165-169 and 1 (2.00%) patient had 170 in Height (cm). In With MS, 13 (26.00%) patients had Missing, 9 (18.00%) patients had 159, 16 (32.00%) patients had 160-164, 7 (14.00%) patients had 165-169 and 5 (10.00%) patients had 170 in Height (cm). In Not Exposed to DMT, 6 (12.00%) patients had Missing, 15 (30.00%) patients had 159, 12 (24.00%) patients had 160–164, 6 (12.00%) patients had 165-169 and 11(22.00%) patients had 170 in Height (cm). In Exposed to DMT, 8 (16.00%) patients had Missing, 10 (20.00%) patients had 159, 6 (12.00%) patients had 160-164, 14 (28.00%) patients had 165-169 and 12(24.00%) patients had 170 in Height (cm).Association of Height (cm) with Maternal and pregnancy characteristics was statistically significant (p = 0.0084).

Pre-pregnancy BMI (kg/m^2): In Without MS, 8 (16.00%) patients had Missing, 7 (14.00%) patients had <18.5, 5 (10.00%) patients had 18.5-24.9, 6 (12.00%) patients had 25.0-29.9, 11 (22.00%) patients had 30.0-34.9, 9 (18.00%) patients had 35.0-39.9 and 4 (8.00%) patients had 40.0 Pre-pregnancy BMI (kg/m^2). In With MS, 6 (12.00%) patients had Missing, 9 (18.00%) patients had <18.5, 11 (22.00%) patients had 18.5-24.9, 7 (14.00%) patients had 25.0-29.9, 4 (8.00%) patients had 30.0-34.9, 5 (10.00%) patients had 35.0–39.9 and 8 (16.00%) patients had 40.0 Pre-pregnancy BMI (kg/m^2). In Not Exposed to DMT, 5 (10.00%) patients had Missing, 7 (14.00%) patients had <18.5, 11 (22.00%) patients had 18.5-24.9, 6 (12.00%) patients had 25.0-29.9, 9 (18.00%) patients had 30.0–34.9, 8 (16.00%) patients had 35.0-39.9 and 4 (8.00%) patients had 40.0 Pre-pregnancy BMI (kg/m^2). In Exposed to DMT, 8 (16.00%) patients had Missing, 6 (12.00%) patients had <18.5, 7 (14.00%) patients had 18.5-24.9, 4 (8.00%) patients had 25.0-29.9, 9 (18.00%) patients had 30.0-34.9, 10 (20.00%) patients had 35.0-39.9 and 6 (12.00%) patients had 40.0 Pre-pregnancy BMI (kg/m^2). Association of Pre-pregnancy BMI (kg/m^2) with Maternal and pregnancy characteristics was not statistically significant (p = 0.9715).

Pre-gestational diabetes: In Without MS, 20 (40.00%) patients had Pre-gestational Diabetes. In With MS, 25 (50.00%) patients had Pre-gestational Diabetes. In Not Exposed to DMT, 26 (52.00%) patients had

Pre-gestational Diabetes. In Exposed to DMT, 27 (54.00%) patients had Pre-gestational Diabetes. Association of Pre-gestational Diabetes with Maternal and pregnancy characteristics was not statistically significant (p = 0.5085).

Pre-gestational hypertension: In Without MS, 23 (46.00%) patients had Pre-gestational Hypertension. In With MS, 29 (58.00%) patients had Pre-gestational Hypertension. In Not Exposed to DMT, 17 (34.00%) patients had Pre-gestational Hypertension. In Exposed to DMT, 37 (74.00%) patients had Pre-gestational Hypertension. Association of Pre-gestational Hypertension with Maternal and pregnancy characteristics was statistically significant (p = 0.0005).

DISCUSSION

This is a Retrospective Cohort Study, It's conducted from 2 year at, Department of Neurology, Super Specialty Hospital, Govt. Medical College Jammu, Jammu and Kashmir, India, 180016. Pregnant women diagnosed with MS who were part of a population-based cohort. 200 patients were included in this study. Fink *et al*.[7] showed that there is a paucity of information on maternal multiple sclerosis (MS) and risk of adverse pregnancy and perinatal outcomes. Compared with offspring of MS-free women, neonates of mothers with MS were at increased risks of medically indicated preterm birth and being born small for gestational age.

In our study, out of 200 patients most of the patients were 25-29 years old [56 (28.00%)] but this was statistically significant (p = 0.0069).

Our study showed that, less number of patients hadCountry of birth missing in Without MS [14 (28.00%)] compared to With MS [19 (38.00%)], Exposed to DMT [20 (40.00%)] and Not Exposed to DMT [21 (42.00%)] but this was not statistically significant (p = 0.0284).

Fink *et al*.[7] showed that there is a paucity of information on maternal multiple sclerosis (MS) and risk of adverse pregnancy and perinatal outcomes. Compared with women without MS, women with MS were, on average, older at the time of delivery, nulliparous, born in the Nordic countries, smoked or were snuff users during pregnancy and had a higher education.

Our study showed that, less number of patients were Education 9 in Exposed to DMT [10(20.00%)] compared to Not Exposed to DMT [18 (16.00%)], With MS[18 (16.00%)] and Without MS[18 (16.00%)] but this was statistically significant (p = 0.1948).

We observed that, more number of patients had Cohabitation with partner in Without MS [20(40.00%)] compared to Not Exposed to DMT [16 (32.00%)], With MS [14 (28.00%)] and Exposed to DMT [14 (28.00%)] but this was not statistically significant (p = 0.0447).

It was found that, higher number of patients were smoker in Without MS [20 (40.00%)] compared to Not Exposed to DMT [19 (38.00%)], Exposed to DMT[16 (32.00%)] and With MS[10(20.00%)] but this was not statistically significant (p = 0.2607).

It was found that, higher number of patients had smoker in Not Exposed to DMT [20 (40.00%)] compared to Exposed to DMT [18 (36.00%)], With MS [16 (32.00%)] and W without MS [13(26.00%)] but this was not statistically significant (p = 0.0002).

In our study, higher number of [21 (42.00%)] patients had Parity in Without MS compared to Not Exposed to DMT [14 (28.0%)], Exposed to DMT [13 (26.00%)] and With MS [12 (24.00%)] but this was not statistically significant (p = 0.24065).

We found that, most number of [16 (32.00%)] patients were Height (cm) 159 in Without MS compared to Not Exposed to DMT [15 (30.00%)], Exposed to DMT [10 (20.00%)] With MS [9(18.00%)] but this was not statistically significant (p = 0.0084).

We observed that, more number of [9 (18.00%)] patients hadPre-pregnancy BMI (kg/m^2) <18.5 in With MS compared to Without MS [7 (14.00%)], Not Exposed to DMT [7 (14.00%)] and Exposed to DMT [6(12.00%)] but this was not statistically significant (p = 0.9715).

It was found that, more number of [27(54.00%)] patients had port Pre-gestational Diabetes in Not Exposed to DMT compared to Not Exposed to DMT [26 (52.00%)]], [25(50.00%)]With MS and Without MS [20(40.00%)] but this was not statistically significant (p = 0.5085).

We examined that, higher number of [37(74.00%)] patients had Pre-gestational Hypertension in Exposed to DMT compared to With MS [29 (58.00%)]], [23(46.00%)] Without MS and Not Exposed to DMT [17(34.00%)] but this was not statistically significant (p = 0.0005).

CONCLUSION

Pregnancy often leads to a reduction in MS disease activity, particularly during the second and third trimesters. This reduction is thought to be related to the immunological changes that occur during pregnancy. The use of certain DMDs during pregnancy can impact both maternal and fetal outcomes. Some DMDs are considered relatively safe, while others are associated with potential risks. The safety profile can vary depending on the specific medication and the timing of exposure. It is often recommended that women with MS who are planning to become pregnant consult with their healthcare providers to discuss the risks and benefits of continuing DMDs. Tailoring treatment plans and monitoring throughout pregnancy are crucial for optimizing outcomes for both mother and baby.

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