Original Research Article

Intravenous immunoglobulin treatment during pregnancy and the post-partum period in women with multiple sclerosis: A prospective analysis

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Abstract

Background: Relapsing-remitting multiple sclerosis (RRMS) affects predominantly young women within reproductive years. As an increased risk of relapses is known to occur during the post-partum period, it is important to consider treatment options.

Aim: Evaluate the effects of intravenous immunoglobulins (IVIg) to prevent post-partum relapses.

Methods: We prospectively followed 198 pregnant female RRMS patients, 67 treated with IVIg during pregnancy and the three months post-partum, and 131 untreated patients that served as controls.

Results: During the pre-gestation year, 41.4% were treated with immunomodulatory drugs, and 28.3% experienced a relapse. During pregnancy and the post-partum period, the number of relapsing patients significantly decreased in the IVIg group (37.3%, 10.4%, 8.9%, respectively, $p = 0.0003$), while no significant change was observed in the untreated group (23.7%, 17.6%, and 22.1%). During the three-month post-partum period, there were only mild and moderate relapses in the IVIg group, while in the untreated group, there were also severe relapses. Stepwise logistic regression that assessed the relation between three-month post-partum relapse and explanatory variables demonstrated that untreated patients had increased risk for post-partum relapse (odds ratio = 4.6, 95% CI [1.69, 12.78], $p = 0.033$).

Conclusions: IVIg treatment proved efficient to reduce the rate and severity of relapses during pregnancy and the three-month post-partum.

Keywords: Multiple sclerosis, Relapse, Intravenous immunoglobulins, Pregnancy, Post-partum

Introduction

Multiple sclerosis (MS) is the most common disease affecting young adults and is more frequent in females during the reproductive years.[1] Therefore, many female MS patients are interested to conceive, give birth, and have a family.

It is well established that the rate of relapse declines during pregnancy especially in the third trimester but increases during the first three months post-partum before returning to the pre-pregnancy rate.[2,3] The increased relapse rate during the post-partum period and the sustained pre-pregnancy year relapse rate during the first and second trimesters of pregnancy prompt serious consideration as to the need for MS patients to be treated during the pregnancy and post-partum period. Moreover, pregnancy-associated relapses were reported to have an impact on disability progression within 12 months post-partum.[4]

The introduction of highly effective immunomodulatory drugs (IMD) for MS opened a new area whereby these treatments served to reduce disease activity and progression.[5,6] However, lack of detailed knowledge regarding their safety during pregnancy led to the advice to discontinue treatments prior to conception. This advice is based on the potential risks to the unborn fetus, including spontaneous abortions and

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congenital malformations.[7,8] Discontinuing treatment with IMD before conception may be associated with rebound disease activity and progression due to the time interval between treatment cessation and conception, when patients are not treated. Extended drug holidays may lead to re-emergence of acute relapses without the possibility of further dosing during pregnancy, especially for highly effective therapies such as rituximab, ocrelizumab, alemtuzumab, or cladribine. Furthermore, discontinuing fingolimod or natalizumab in order to conceive was reported to be associated with disease reactivation during the conception period or pregnancy.[9] Therefore, the possibility to treat MS using a pregnancy-safe medication is of great importance. Intravenous immunoglobulin (IVIg) treatment has been used to reduce post-partum relapse rates in women with relapsing remitting MS (RRMS). We have previously reported a noteworthy therapeutic effect of IVIg treatment on the reduction of relapse rate in a small group of MS patients during pregnancy and the post-partum period.[10] Patients treated for the whole pregnancy and post-partum period had significantly fewer relapses than untreated pregnant patients. The rationale for such practice evolved from studies showing the benefits of IVIg for reducing relapse rates in RRMS.[11–13] Moreover, IVIg treatment can be used unhesitatingly during pregnancy and lactation with no safety concerns, and the treatment is known to have protective immune benefits for the fetus, the newborn and the mother as well.[14] These benefits are related to multiple effects on the immunoregulatory network affecting T-cell responses, complement activation, FcRn saturation, FcγRIIb receptors, and cytokines in various autoimmune diseases.[15]

In the current study, we prospectively followed a large cohort of pregnant MS patients and systematically evaluated the effect of IVIg treatment on relapses during pregnancy and the post-partum period in comparison to untreated patients and assessed the effect of various variables on relapse rates.

Methods

Study design
Prospective observational study. MS patients followed at the Sheba Multiple Sclerosis Center that gave birth between 01 January 2016 to 31 December 2021 were included in the study. Patients were either untreated during the pregnancy and the post-partum period or received IVIg 0.4 g/kg body weight/day for 5 consecutive days as a loading dose with additional booster doses of 0.4 g/kg body weight/day once every six weeks. IMD treatments were stopped when patients decided to conceive according to each drug recommendation, and for treatment-eligible patients, IVIg treatment was initiated at least three months prior to conception and continued up to three months post-partum. The decision to treat patients with IVIg was based on the patient's willingness and the approval of the health insurance provider to supply the treatment. In our MS Center, we take a specific approach to explain to female patients the risk of post-partum relapse and treatment choices as well as the possibility to switch/stop previous IMD before conception. Moreover, in our team, we have a specialist in obstetrics and gynecology (MSK) that routinely provides consulting encounters to patients before and during pregnancy. It is possible that patients that relapsed in the year prior to the pregnancy were more willing to receive IVIg treatment. However, as the approval of the health insurance provider to supply the treatment was also a limiting factor even when the patient consent; there was no pre-conception bias in the selection of patients to receive IVIg treatment. The study was approved by the Sheba Institution Review Board. All patients gave written informed consent to receive IVIg treatment.

Patients
Pregnant RRMS female patients followed at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel, were included in the study. Eligible patients were diagnosed with MS according to 2010 revised McDonald criteria[16] and had a relapsing-remitting disease course. Acute relapse was defined as the onset of new neurological symptoms or worsening of existing ones that persisted for at least 48 h associated with objective findings in the clinical neurological examination manifested by an increase in the Expanded Disability Status Scale (EDSS) score.[17] The change from a previous EDSS score performed prior to the acute relapse, while the patient was in remission, to the relapse score, was used to determine the severity of the relapse. Severe relapses were defined by an increase of at least 2.0 EDSS points; moderate relapses were defined as an increase of 1.0 or 1.5 EDSS points; and mild relapses were defined by an increase of 0.5 EDSS points.[18] EDSS was assessed once every three months during the study period and at the time of a suspected relapse. Breast feeding was considered positive when patients' breastfed for more than two consecutive weeks following delivery during the three months post-partum.

Statistical analysis

Categorical variables are described by giving sample size, frequency, and percentage by study group. Continuous variables are reported by sample size, arithmetic mean and SD, median and 25–75 interquartile range values. Comparison between groups was calculated for the differences between qualitative variables using the chi-square test, and for differences between the quantitative variables using the parametric independent t-test and non-parametric Mann-Whitney test. Logistic regression model using stepwise method was applied for testing the relation between post-partum relapse and explanatory variables including treatment group, previous IMD treatment, mother age at birth, disease duration, pregnancy relapses and relapse during the pre-gestation year. Odds ratios were estimated via the final logistic model. The regression models were repeated in the subgroup of patients that were not treated during the pregnancy and post-partum period. ANOVA with repeated measurements was applied to evaluate the risk of relapses during and after pregnancy.

All tests were two-tailed and a p value <0.05 or less was considered statistically significant. Data were analyzed using the SAS® version 9.4 (SAS Institute, Cary North Carolina) and Python software (version 3.0).

Results

Patients characteristics

A total of 198 pregnant female RRMS patients, 67 treated with IVIg before conception, during pregnancy and up to three months following delivery, mean ± SD age 32.6 ± 5.5 years, disease duration 7.2 ± 4.4 years, IVIg treatment duration prior to pregnancy was 2.0 ± 2.5 years, median 1.0 years, and 131 MS patients similarly followed without receiving immunomodulatory treatment during pregnancy and up to three months following labor, age 32.9 ± 4.9 years, disease duration 7.8 ± 4.5 years, were included in the study. In the year prior to becoming pregnant, 41.4% were treated with IMD, and 28.3% experienced a relapse during the pre-gestation year. Specifically, 45/67 (67.2%) of patients treated with IVIg, and 37/131 (28.2) of untreated patients received IMD prior to the pregnancy, and the time between stopping IMD and pregnancy was 2.3 ± 2.2 years, median 1.1 years. The demographics, clinical variables and various IMD treatments of the study participants are presented in Table 1.

Pregnancy and post-partum related variables

During the pre-gestation year, 37.3% of patients that initiated IVIg treatment and 23.7% of untreated patients experienced a relapse, $p = 0.18$. Lower relapse rates were observed during pregnancy. During the post-partum period, there were 35 relapses, six relapses (17.1%) occurred in the IVIg-treated group, and 29 relapses (82.9%) in the untreated group, $p = 0.0001$. The number of relapsing patients significantly decreased in the IVIg group from 37.3% in the pre-gestation year to 10.4% during pregnancy, and 8.9% in the post-partum period, $p = 0.0003$, while no significant decrease was observed in the untreated group (23.7%, 17.6%, and 22.1%, respectively). Between-group comparison demonstrated a significant difference in the number of post-partum relapsing patients; 8.9% in the IVIg-treated patients vs. 22.1% in the untreated group, $p = 0.021$. The pattern of relapse severity in the post-partum period differed between the groups; there was 1 (1.5%) mild, 5 (7.5%) moderate, and no severe relapses in the IVIg group, while in the untreated group 5 (3.8%) relapses were mild, 14 (10.7%) moderate, and 10 (7.6%) severe relapses. Disability by EDSS during post-partum relapse was 2.5 ± 1.3 in the IVIg-treated group as compared to 3.4 ± 1.5 in the untreated group. No significant difference was found in the rate of breast-feeding during the post-partum period between groups. Data are presented in Table 1 and Figure 1.

Post-partum variables in the subgroup of untreated MS patients

Analysis of the 131 MS patients that were not treated during the pregnancy and the post-partum period, disclosed that 22.1% had a post-partum relapse. These subjects did not differ from untreated patients that did not experience a relapse during the post-partum period in age at delivery and disease duration. However, more post-partum relapsing patients received IMD treatment prior to gestation (58.6% vs. 19.6%, $p = 0.001$), and this group had higher rates of relapses during pregnancy (34.5% vs. 20.6%, $p = 0.007$), and higher disability by the EDSS prior to gestation (median 2.7 ± 1.87 vs. 1.6 ± 1.34, $p = 0.005$); Data are presented in Table 2 and Figure 2.

Prediction of post-partum relapse

A repeated measures ANOVA demonstrated a statistically significant difference in the risk of pregnancy and post-partum relapses ($p = 0.003$) between the IVIg treated and untreated groups.

Table 1. Demographic, clinical, and labor-related variables.

Study population	MS pregnancies			
	All N = 198	Untreated N = 131, 66.2%	IVIg-treated N = 67, 33.8%	p
Age at delivery, years				
Mean ± SD	32.8 ± 5.12	32.9 ± 4.92	32.6 ± 5.51	0.73
Median	32.2	32.1	32.5	
25–75 IQR	29.9–36.1	29.8–35.8	30.1–36.5	
Disease duration, years				
Mean ± SD	7.6 ± 4.47	7.8 ± 4.49	7.2 ± 4.44	0.36
Median	6.6	7.2	6.4	
25–75 IQR	3.8–10.3	3.9–10.6	3.5–9.6	
Disability by EDSS				
Median	1.0	1.5	1.0	0.12
25–75 IQR	1.0–2.0	1.0–2.0	1.0–1.5	
Previous IMD during the year preceding pregnancy				
N, %	82, 41.4	37, 28.2	45, 67.2	0.0008
IMD prior to pregnancy, N, %				
Alemtuzumab	1, 0.5	1, 0.8	0	
Dimethyl fumarate	23, 11.6	23, 17.6	0	
Glatimarer acetate	10, 5.1	6, 4.6	4, 6.0	
Fingolimod	5, 2.5	0	5, 7.5	
Beta-interferons	26, 13.1	0	26, 38.8	
Natalizumab	14, 7.1	5, 3.8	9, 13.4	
Teriflunomide	2, 1.0	2, 1.5	0	
Relapses during the year preceding pregnancy				
N, %	56, 28.3	31, 23.7	25, 37.3	0.177
Relapses during pregnancy				
N, %	30, 15.2	23, 17.6	7, 10.4	0.186
Relapses during 3-months post-partum				
N, %	35, 17.7	29, 22.1	6, 8.9	0.021
Post-partum relapse severity				
N, %	140, 70.7	91, 69.5	49, 73.3	0.591
Mild	6, 17.1	5, 17.2	1, 16.7	0.202
Moderate	19, 54.3	14, 48.3	5, 83.3	
Severe	10, 28.6	10, 34.5	–	
Time to post-partum relapse, months				
Mean ± SD	1.5 ± 0.5	1.6 ± 0.68	1.2 ± 0.38	0.46
Median	1.5	1.5	1.2	
25–75 IQR	1.1–2.0	1.07–2.18	0.97–1.53	
Relapse EDSS, N	35	29	6	
Mean ± SD	3.2 ± 1.5	2.5 ± 1.3	3.4 ± 1.5	0.23
Median	3.0	3.0	2.0	
25–75 IQR	2.0–4.0	2.5–4.0	2.0–2.4	
Breast feeding during the post-partum period, N, %	60, 30.3	38, 29	22, 32.8	0.103

Stepwise logistic regression that assessed the relation between post-pregnancy relapse and explanatory variables demonstrated that there was a significant difference in the odds ratio of post-partum relapse between patients that received IVIg treatment and patients that were not treated (odds ratio = 4.6, 95% CI [1.69, 12.78], $p = 0.033$) after correction for IMD treatment during the year prior to the pregnancy, suggesting that
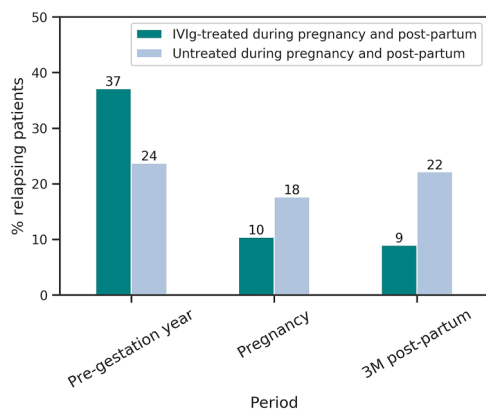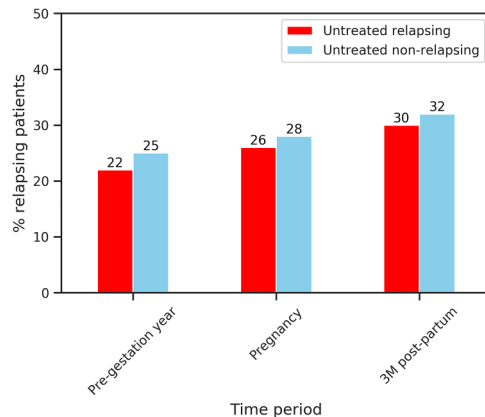
Figure 1. Percent of relapsing patients before, during and after pregnancy.

untreated patients had 4.6 times increased risk for post-partum relapse as compared to patients treated with IVIg. Other additional important independent variables, mother age at birth (odds ratio = 1.06, 95% CI [0.95, 1.18], $p = 0.27$), disease duration at birth (odds ratio = 0.98, 95% CI [0.87, 1.09], $p = 0.65$), and last EDSS before pregnancy (odds ratio = 0.67, 95% CI [0.50, 0.89], $p = 0.06$), were not statistically different between the groups. Evaluation of the risk for post-partum relapse within the untreated patient group, disclosed that the major contributing variable was IMD treatment during the pre-gestation year (odds ratio = 2.7, 95% CI [1.02, 7.24], $p = 0.046$), suggesting that patients that were not treated prior to pregnancy had an increased risk by 2.7 times to develop post-partum relapse as compared to patients that were treated during the pre-pregnancy year.

Table 2. Demographic, clinical, and labor-related variables in untreated MS patients during pregnancy and post-partum by post-partum relapse.

Variable	Post-partum relapse = YES N = 29, 22.1%	Post-partum relapse = NO N = 102, 77.9%	p
Age at delivery, years			
Mean ± SD	33.1 ± 3.93	32.8 ± 5.19	0.81
Median	32.9	31.5	
25–75 IQR	30.6–35.7	29.7–36.1	
Disease duration, years			
Mean ± SD	7.9 ± 4.06	7.7 ± 4.62	0.86
Median	7.8	6.5	
25–75 IQR	5.8–10.4	3.9–11.1	
Disability by EDSS			
Mean ± SD	2.7 ± 1.87	1.6 ± 1.34	0.005
Median	2.0	1.0	
25–75 IQR	1.5–3.5	1.0–2.0	
Previous IMD N, %	17, 58.6	20, 19.6	0.001
Relapses during the year preceding pregnancy, N, %	31, 23.7	25, 37.3	0.45
Pregnancy relapses pregnancy, N, %	10, 34.5	21, 20.6	0.007
Post-partum relapse severity, N, %			
Mild	5, 17.2	–	
Moderate	14, 48.3		
Severe	10, 34.5		
Time to post-partum relapse, months			
Mean ± SD	1.6 ± 0.68	1.2 ± 0.38	0.19
Median	1.5	1.2	
25–75 IQR	1.07–2.18	0.97–1.53	
Relapse EDSS			
Median	3.0	–	
25–75 IQR	2.5–4.0		

Figure 2. Percent of relapsing and non-relapsing patients before, during and after pregnancy in the untreated group.

Adverse events

No serious adverse events were recorded in the IVIg-treated patients. Adverse events judged to be IVIg related included: headaches (6.0%), rash involving the face and arms (7.5%), and pain at the infusion site (7.5%). These adverse events occurred during the IVIg loading-dose period, responded to analgesics or lowered infusion rate, and resolved within to 24 h. Laboratory blood tests were within normal range except for iron deficiency anemia that occurred in eight patients in the IVIg group and in 19 patients in the untreated group, and was corrected with supplementary iron.

Pregnancy outcome

All women delivered live births, no early or late abortions were observed. Percent of cesarean sections was similar between groups. All neonates had normal physical examinations at the nursery.

Discussion

In the current study, we demonstrated a noteworthy therapeutic effect of IVIg treatment on the reduction of relapses in a prospective study that included a large cohort of RRMS patients during pregnancy and the three-month post-partum period. It is evident that not all pregnant women will relapse during the post-partum period. In our cohort, only 22.2% of the pregnant MS patients that were not treated during pregnancy, relapsed in the post-partum period. These findings are similar to the findings reported more than two decades ago in the Pregnancy in Multiple Sclerosis (PRIMS) study, in 1998 and 2004, showing that only 27.7% of the patients experienced relapse during the three-month post-partum period.[2,19] In our study, we characterized these relapsing patients showing that post-partum

relapses were more frequent in women with active disease prior to gestation. These women were more frequently (58.6%) treated with IMD as compared to the non-relapsing patients. The re-occurrence of the disease once IMD was stopped was manifested during the pregnancy period and the post-partum period by a higher prevalence of relapses. However, we found that patients that were not treated with IMD in the year prior to gestation had 2.7 times increased risk to experience a post-partum relapse. This finding is in accordance with a study that showed a lower post-partum relapse rate in patients that received IMD before the pregnancy or during early pregnancy as compared with untreated patients.[3,20] Similarly, in the MSBase registry comprising 893 pregnancies, IMD use in the two years preceding conception was independently associated with a decreased post-partum relapse rate.[21]

Patients treated for the whole pregnancy and post-partum periods with IVIg had significantly fewer relapses with lower relapse severity during the pregnancy and post-partum period as compared with patients that were not treated. We demonstrated that IVIg treatment significantly decreased the risk by 4.6 times for a post-partum relapse as compared with untreated patients, after correction for treatment with IMD prior to the pregnancy. These findings strengthen previous studies suggesting that IVIg can reduce post-partum disease activity in MS patients. A retrospective study reported on 42 pregnant MS patients that received 10 g IVIg for three consecutive days followed by monthly IVIg doses for five months, reported that the three-month post-partum relapse rate was significantly lower for patients who received IVIg as compared with the PRIMS study (0.48 vs 1.2, respectively) for untreated patients.[22] Similarly, we have previously shown in several studies that post-partum IVIg treatment was beneficial in preventing acute childbirth-associated exacerbations in patients with RRMS.[10,23,24]

The reduction in immune activation induced by IVIg can be related to several mechanisms including modulation of cytokine antagonists, interference with T cell proliferation, and long-term selection of immune repertoires.[25] IVIg has been found to protect against experimental autoimmune encephalomyelitis,[26] and this beneficial effect was associated with decreased proliferation of T cells specific for the immunizing antigen and the expansion of regulatory T cells.[27,28]

To conclude, our findings highlight the beneficial approach of treatment with IVIg in active MS patients

during pregnancy and the post-partum period. This well-tolerated and fetus-safe treatment can replace IMD treatment and serve as IMD-sparing treatment for the pregnancy and post-partum period.

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