

RESEARCH ARTICLE

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Pregnancy and Disease Activity in AQP4+ Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease: A Multicenter Turkish Cohort

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ABSTRACT

Introduction: The impact of pregnancy on relapse activity and disability progression in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has not been fully clarified. In this study, we aimed to evaluate the impact of pregnancy on disease activity and disability in AQP4-Ab+ NMOSD and MOGAD and also to assess the effect of these two disorders on obstetric outcomes.

Methods: A retrospective longitudinal multicenter study of 71 women (AQP4-Ab+ NMOSD: 55; MOGAD: 16) were analyzed. Linear mixed-effects models were used to assess longitudinal changes in Expanded Disability Status Scale (EDSS) and annualized relapse rate (ARR) across pregnancy-related time points (pre-pregnancy, during pregnancy, postpartum).

Results: Expanded disability status scale (EDSS) remained stable during pregnancy but increased at last follow-up for both groups (for NMOSD

p=0.002, for MOGAD p=0.042). Higher pre-pregnancy ARR and younger maternal age predicted greater postpartum disability in AQP4-Ab+ NMOSD patients, while for MOGAD patients, pre-pregnancy ARR was associated with later EDSS worsening. No significant change in ARR was observed across pregnancy-related periods in either group. Obstetric complications were rare. Miscarriage rates were low in both groups (AQP4-Ab+ NMOSD: 1.8%, MOGAD: 6.2%), with no major neonatal abnormalities.

Conclusion: Pregnancy was not associated with an increased relapse rate but was followed by long-term EDSS worsening in both NMOSD and MOGAD, particularly in patients with high pre-pregnancy disease activity. Obstetric outcomes were generally favorable.

Keywords: annualized relapse rate, disability progression, myelin oligodendrocyte glycoprotein antibody-associated disease, neuromyelitis optica spectrum disorder, pregnancy

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Highlights

- Pregnancy did not increase relapse rates in NMOSD or MOGAD.
- Disability remained stable during pregnancy but worsened postpartum.
- High pre-pregnancy relapse rate predicted later disability in both groups.
- Obstetric outcomes were favorable, but cesarean delivery rates were high.

INTRODUCTION

Aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-Ab+ NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are rare, antibody-mediated demyelinating disorders of the central nervous system, primarily affecting the optic nerves and spinal cord (1). AQP4-Ab+ NMOSD shows a strong female predominance, with a female-to-male ratio up to 9:1, particularly around the age of 30. Myelin oligodendrocyte glycoprotein antibody-associated disease presents more evenly but still affects women slightly more often in adult-onset cases (2). While MOGAD is more common in children and young adults, NMOSD often appears in older women, though nearly half are diagnosed before age 40. As both conditions frequently affect women of reproductive age, their interaction with pregnancy, both in terms of disease activity and pregnancy outcomes, raises important clinical considerations (3,4).

Pregnancy in patients with NMOSD is considered high-risk due to a greater incidence of obstetric complications and a heightened risk of relapse, especially in the postpartum period (5). Additionally, over 20% of NMOSD patients have coexisting autoimmune conditions, which may further compromise pregnancy outcomes (6). In contrast, data on the impact of pregnancy in MOGAD are limited, and no consensus has been reached regarding the extent of risk. However, given that disability in both conditions is primarily relapse-driven, vulnerability during pregnancy is compounded by both disease activity and therapeutic restrictions during gestation. These challenges indicate the need for further research to guide clinical decision-making and improve perinatal management.

This multicenter study aims to evaluate and compare the impact of pregnancy on relapse activity and disability progression in patients with NMOSD and MOGAD during pregnancy and the postpartum period. In parallel, it assesses the effect of these conditions on pregnancy outcomes, including obstetric complications, delivery characteristics, and neonatal health.

METHODS

Study Design

This retrospective longitudinal multicenter study was conducted under the coordination of the Neuroimmunology Working Group of the Turkish Neurological Society. Data were collected from 17 centers across different regions of Türkiye. Each center extracted clinical and demographic information from its institutional patient database or electronic medical record system. All data were anonymized before being merged for analysis. Patients who were eligible with the 2015

international consensus diagnostic criteria for NMOSD and the 2023 international MOGAD panel proposed criteria were included in the study (1,7).

Relapses were defined as the occurrence of new or worsening neurological symptoms lasting at least 24 hours. Any new symptom within four weeks was considered a part of the same episode. To monitor disability progression, Expanded Disability Status Scale (EDSS) scores were analyzed across four time points for only the first pregnancy after the diagnosis: preconception (baseline–within 3 months prior to conception), during pregnancy (The highest EDSS score measured during pregnancy), one year postpartum, and most recent follow-up (The highest EDSS score between the first and second years after birth). For the annualized relapse rate (ARR) analysis, three periods were defined based on the first pregnancy after the diagnosis: one year before conception (pre-pregnancy), duration of pregnancy, and one year postpartum.

This study was approved by the Clinical Research Ethics Committee of İzmir Katip Çelebi University (2023/350).

Patient Characteristics

The study aimed to investigate the effect of pregnancies occurring after diagnosis on disease outcomes. Therefore, only female patients with a history of at least one post-diagnosis pregnancy were included. Patients were excluded if they had seronegative NMOSD, other concomitant autoimmune diseases, obstetric conditions that could independently affect pregnancy outcomes, or incomplete/inconsistent medical records.

Statistical Analysis

All statistical analyses were conducted using R version 4.4.1. Analyses were performed separately for patients with AQP4-Ab+ NMOSD and MOGAD who had experienced at least one pregnancy. Demographic data (current age, age at first symptom, age at first pregnancy, and disease duration) were presented as median and interquartile range (IQR). Comparisons of continuous variables were performed by Mann-Whitney U Test.

For each diagnostic group (NMOSD and MOGAD), a linear mixed-effects model (LMM) was fitted with EDSS as the dependent variable, time point as a fixed effect, and patient identification number as a random intercept to account for within-subject correlation. Age at pregnancy and preconception ARR were included as covariates. The models were fitted using restricted maximum likelihood with Satterthwaite-approximated degrees of freedom for fixed effects.

To visualize EDSS trajectories, both boxplots and estimated marginal means derived from the LMMs were used. Marginal predictions and 95% confidence intervals were extracted and plotted, overlaying individual EDSS values and model-based predictions.

RESULTS

Demographic and Clinical Data

A total of 71 women with AQP4-Ab+ NMOSD (n=55) or MOGAD (n=16) were included in the study. No significant difference was observed in the age at symptom onset between the groups and the age at first pregnancy. However, disease duration before the first pregnancy was longer in the NMOSD group compared to the MOGAD group [9 (5–17) vs. 5 (3.5–8); p=0.02] (Table 1).

Table 1. Demographic and clinical characteristics of patient groups

Characteristic	AQP4-Ab+ NMOSD (n=55)	MOGAD (n=16)	p
Age at disease onset	28 (23–33)	28 (24–31)	0.9
Age at first pregnancy	34 (30–39)	33 (29–36)	0.6
Disease duration before pregnancy (years)	9 (5–17)	5 (3.5–8)	0.02*

Statistical comparisons are performed using the Mann-Whitney U test. Values are presented as median (IQR). *p-values <0.05 are highlighted in bold.

Table 2. Adjusted mean EDSS scores across four different time points in relation to pregnancy

	Time point	Adjusted mean	95% CI	p-value (vs. Baseline)
NMOSD	Baseline	1.6	0.9 – 2.3	
	Pregnancy	2.0	1.3 – 2.8	0.4
	1-year postpartum	2.2	1.5 – 3.0	0.07
	Follow-up	2.5	1.8 – 3.3	0.002
MOGAD	Baseline	1.0	0.4 – 1.7	
	Pregnancy	1.4	0.8 – 2.1	0.6
	1-year postpartum	1.6	1.0 – 2.3	0.1
	Follow-up	1.8	1.1 – 2.4	0.042

Values are derived from linear mixed-effects models adjusted for age at first pregnancy and pre-pregnancy ARR. P-values are Bonferroni-adjusted for three comparisons per group.

Effect of Pregnancy on Disease Activity

According to the linear mixed-effects model, the adjusted mean EDSS during pregnancy was not significantly different from baseline in either group: NMOSD: 2.0 vs. 1.6 ($p=0.4$) and MOGAD: 1.4 vs. 1.0 ($p=0.6$) (Table 2). In the NMOSD cohort, the mean EDSS rose to 2.2 at one year postpartum ($p=0.07$) and to 2.5 at the last follow-up ($p=0.002$), indicating a significant long-term increase. Younger age at first pregnancy and higher pre-pregnancy ARR remained independently associated with greater postpartum EDSS worsening (both $p < 0.001$). In the MOGAD cohort, the adjusted mean EDSS increased to 1.6 at one year postpartum ($p=0.1$) and to 1.8 at the last follow-up ($p=0.04$). Age at first pregnancy was not related to EDSS change ($p=0.3$), whereas a higher pre-pregnancy ARR was strongly associated with higher EDSS at follow-up ($p < 0.001$) (Figure 1).

As presented in Table 3, according to LMM, no significant change in ARR was observed across pregnancy-related time points in either diagnostic group. Age at first pregnancy and baseline EDSS were not significantly associated with ARR (Figure 2).

Effect of Disease on First Pregnancy

In the NMOSD group, one patient (1.8%) experienced a spontaneous abortion during her first pregnancy after diagnosis, and another patient developed preterm labor at 36+2 weeks, followed by low birth weight. In the MOGAD group, one patient experienced preterm labor at 36+4 weeks with low birth weight, while another patient had a newborn with neonatal jaundice. In the MOGAD group, one (6.2%) spontaneous abortion was reported. Apart from the mentioned complications, no other pregnancy-related complications were observed.

The median gestational duration was 38 weeks in both disease groups [NMOSD: 38 (IQR: 38–39), MOGAD: 38 (IQR: 37–39)]. Cesarean delivery was performed in 32 (58.2%) of pregnancies in the NMOSD group and 11 (68.8%) of those in the MOGAD group.

Treatment Data

Intravenous methylprednisolone was the primary treatment modality for managing acute relapses during pregnancy in both cohorts, administered to all 11 NMOSD patients and two MOGAD patients who experienced relapses. One NMOSD patient additionally received plasma exchange in combination with IV methylprednisolone. No patients received intravenous immunoglobulin, eculizumab, or other escalation therapies during pregnancy.

Before conception, azathioprine was the most frequently prescribed immunosuppressant in both groups, administered to 55.8% of NMOSD and 42.9% of MOGAD patients. Rituximab was used in 21.1% of NMOSD and 21.4% of MOGAD patients, while oral corticosteroids were prescribed in 23.1% and 35.7%, respectively. None of the patients received mycophenolate mofetil, eculizumab, tocilizumab, or cyclophosphamide in the preconception period. Among 40 NMOSD patients with available data on treatment modification, 31 (77.5%) discontinued immunotherapy according to a preplanned schedule, with a median interval of three months before conception (IQR: 2–4), while the remaining nine patients (22.5%) ceased treatment following pregnancy confirmation. In the MOGAD group, preconception treatment history was available for five patients; of these, four (80%) discontinued therapy in a planned manner, with a median interval of two months before conception (IQR: 1–4).

During pregnancy, among 19 NMOSD patients with available data, 12 (63.2%) received no immunosuppressive therapy. Four patients (21.0%) were treated with low-dose oral corticosteroids and three (15.8%) with azathioprine. In contrast, among five MOGAD patients with available data, one (20%) received low-dose corticosteroids, while the remaining four (80%) received no treatment. No patients in either group were treated with biologics or high-risk immunosuppressants during gestation.

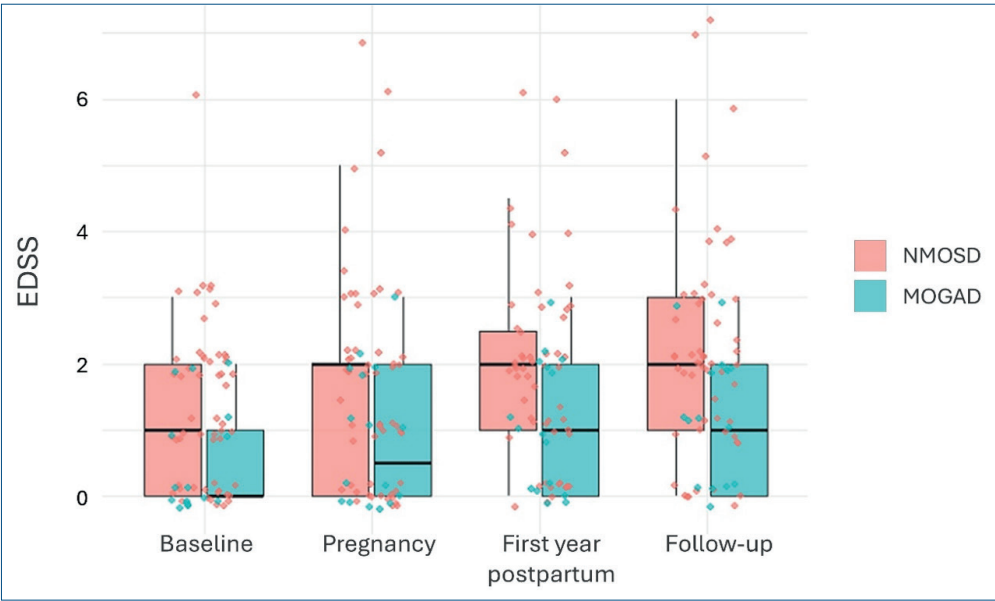


Figure 1. Changes in disability over pregnancy-related time points in AQP4-Ab+ NMOSD and MOGAD. Boxplots show Expanded Disability Status Scale (EDSS) scores at baseline, during pregnancy, at 1 year postpartum, and at the last follow-up, stratified by disease group. Individual data points are overlaid on the boxplots (EDSS: expanded disability status scale; NMOSD: neuromyelitis optica spectrum disorder; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease).

Table 3. Adjusted mean annualized relapse rates (ARR) in the NMOSD and MOGAD groups

		Adjusted Mean ARR	95% CI	Pairwise Comparison	p-value
NMOSD	Pre-pregnancy	0.20	0.05 to 0.35	Pre-pregnancy vs Pregnancy	>0.05
	Pregnancy	0.20	0.05 to 0.35	Pre-pregnancy vs Postpartum	>0.05
	Postpartum	0.24	0.08 to 0.40	Pregnancy vs Postpartum	>0.05
MOGAD	Pre-pregnancy	0.23	-0.05 to 0.52	Pre-pregnancy vs Pregnancy	>0.05
	Pregnancy	0.21	-0.08 to 0.49	Pre-pregnancy vs Postpartum	>0.05
	Postpartum	0.25	-0.06 to 0.56	Pregnancy vs Postpartum	>0.05

Adjusted means are derived from linear mixed-effects models controlling for age at first pregnancy and baseline EDSS. Pairwise comparisons are Bonferroni-adjusted.

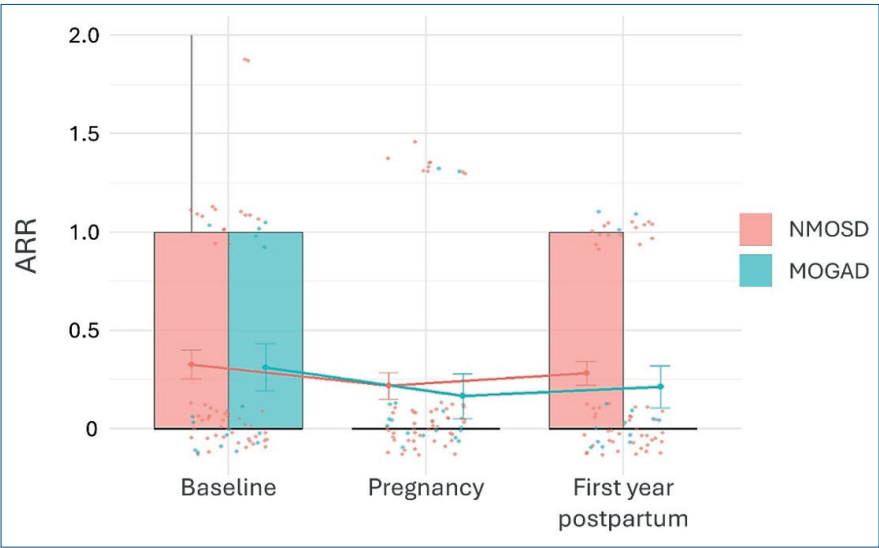


Figure 2. Annualized relapse rates before, during, and after pregnancy in AQP4-Ab+ NMOSD and MOGAD. Annualized relapse rates are presented for the pre-pregnancy baseline period, pregnancy, and the first postpartum year, stratified by disease group. Individual patient values and group-level estimates are shown (ARR: annualized relapse rate; NMOSD: neuromyelitis optica spectrum disorder; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease).

DISCUSSION

There is well-established evidence regarding the effect of pregnancy and the postpartum period on relapses in MS (8). Emerging data from various studies have defined pregnancy outcomes in NMOSD and, more recently, in MOGAD (9). The vast majority of these studies have focused primarily on relapse rates. In this study, we aimed to go beyond relapse data and investigate the impact of pregnancy and the postpartum period on disability progression, as measured by EDSS, in both AQP4-Ab+ NMOSD

and MOGAD. An additional objective was to examine the influence of these diseases on the pregnancy course, delivery method, gestational duration, and fetal/neonatal outcomes. This study was methodologically confined to the initial pregnancy following disease diagnosis and the subsequent postpartum phase.

Previous studies identified various risk factors for pregnancy-related attacks. While Wang et al. reported younger gestational age, inadequate immunotherapy, and high anti-AQP4 titers as risk factors

(10), Shimizu et al. found increased risk with recent relapses and reduced immunosuppression (11). According to Kim et al., treatment discontinuation was associated with increased risk, while rituximab was protective (12). Collongues et al. demonstrated that immunotherapy reduced relapse risk during pregnancy and postpartum, particularly in AQP4-Ab-positive patients; no relapses were observed in untreated MOG-Ab or double-negative cases, though numbers were limited (13). Our study showed that age at first pregnancy and baseline EDSS had no impact on annualized relapse rate (ARR) across different periods in both AQP4-Ab+ NMOSD and MOGAD groups.

In our study, EDSS scores at one year postpartum were elevated compared to both preconception and pregnancy time points. Among AQP4-Ab+ NMOSD patients, younger maternal age at first pregnancy and higher pre-pregnancy ARR were significant predictors of greater disability in the postpartum period. These findings are consistent with those of Huang et al., who reported stable EDSS scores during pregnancy with subsequent postpartum worsening (5). Similarly, Wang et al. observed increased EDSS values during both pregnancy and postpartum compared to the year preceding conception in AQP4-Ab+ NMOSD patients (10).

Myelin oligodendrocyte glycoprotein antibody-associated disease patients had statistically higher EDSS at follow-up period when compared to baseline EDSS. Unlike AQP4-Ab+ NMOSD patients, only pre-pregnancy ARR predicted worse disability. Previous studies have primarily focused on ARR, and the EDSS data is scarce. Inclusion of longitudinal EDSS analysis, particularly in MOGAD patients, represents a novel aspect of this study.

A clear dissociation between relapse frequency and disability progression emerged in both cohorts, as EDSS scores increased significantly during the postpartum and follow-up periods despite stable ARR across pregnancy-related intervals. This divergence may reflect the occurrence of more severe relapse phenotypes triggered by pregnancy or suboptimal recovery from relapses during this period, potentially due to treatment limitations or physiological changes associated with gestation and the puerperium.

We observed low rates of spontaneous abortion in the NMOSD group compared to those reported in the general population (~15%) (14), suggesting no increased risk. This may be attributed to closer medical monitoring of pregnancies after diagnosis. This finding contrasts with previous studies that reported spontaneous miscarriage rates ranging from 11% to 13% in AQP4-Ab+ NMOSD patients (13,15–17). In our cohort, the miscarriage rate in MOGAD patients (6.2%) was also lower than in the general population (14). Similarly, Carra-Dallière et al. reported 4% fetal demise (one miscarriage and one elective abortion) (3) in MOGAD patients.

Our study revealed a high rate of cesarean section in both disease groups, performed in 58.2% of pregnancies in the NMOSD cohort and 68.8% in the MOGAD group. These rates exceed the national average in Türkiye, which ranged between 50–55% in 2021 (18). These higher cesarean rates may be attributed to neurological disability, concerns about relapse during delivery, or precautionary decisions by obstetricians.

In the literature, preterm birth, low birth weight, intrauterine growth restriction, preeclampsia, and gestational hypertension have been reported in patients with AQP4-Ab+ NMOSD. In our cohort, preterm birth and low birth weight were reported in two cases across both groups, with no notable neonatal abnormalities detected. For the MOGAD group, evidence regarding fetal anomalies or systemic neonatal

pathologies remains limited (3,19). In our MOGAD group, one patient also experienced preterm labor at 36+4 weeks with low birth weight, while another patient had a newborn with neonatal jaundice.

This study has several limitations. First, it is retrospective, and missing data were collected through phone calls or e-mails. Second, breastfeeding data were not available. Third, the study did not measure AQP4-IgG levels; therefore, antibody titers could not be correlated with pregnancy outcomes. Fourth, a very limited number of patients received immunosuppressive therapy during pregnancy. Although the absence of treatment did not lead to an increase in the frequency of relapses during pregnancy, it can be said that more data are needed regarding its association with an increase in long-term disability. In addition, the underlying factors contributing to delivery choice were not systematically analyzed in this cohort.

Our results indicate that pregnancy may have a long-term impact on functional decline for both disorders. This multicenter cohort offers valuable comparative insights into the relationship between pregnancy and disease activity in AQP4-Ab+ NMOSD and MOGAD groups. Annualized relapse rate did not change across different pregnancy-related time intervals in either group. Pregnancy-related complications were relatively low, and the cesarean delivery rate was high in both disorder groups. By representing pregnancy-related outcomes of NMOSD and MOGAD cohorts together, our findings reinforce and extend existing literature (9,20,21). We believe that this retrospective longitudinal assessment will be valuable for patients planning pregnancy. Our findings underscore the importance of individualized preconception counseling and close postpartum monitoring, especially in patients with active disease before pregnancy.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of İzmir Katip Çelebi University (2023/350).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- CU, AT, MK; Design- CU, AT, MK, YB; Supervision- ÖFT, HE, YB, RK, MK, AT; Resource- CU, AT; Materials- SD, MT; Data Collection and/or Processing- MÇ, SŞ,AA, SDB, GAD, BPB, EG, RK, TG; Analysis and/or Interpretation- GA, HG, PAÖ, OCZ, MFY, CB; Literature Search- GGC, MK, SG, NY, SS; Writing- CU, AT, MK; Critical Reviews- TG, HG, SD, AT, MK.

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Data Availability Statement: The data that supports the findings of this study is not openly available due to patient data privacy, but it is available from the corresponding author upon reasonable request.

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