RESEARCH ARTICLE

Effects of pregnancy on neuromyelitis optica spectrum disorder and predictors of related attacks

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Abstract

Objective: Our study aimed to investigate the influence of pregnancy on the course of neuromyelitis optica spectrum disorders (NMOSD) and to explore the independent predictors of pregnancy-related attacks. Methods: We performed a retrospective study of patients with NMOSD based on the Wingerchuk 2006 or the revised Wingerchuk 2015 criteria. Demographic, clinical, and pregnancy data were recorded. We compared the annualized relapse rate (ARR) before, during, and after pregnancy. The Expanded Disability Status Scale (EDSS) score was used to assess the degree of disability. Multivariate Cox proportional hazards models were used to identify the independent risk factors that predict pregnancy-related attacks. Results: There were 202 informative pregnancies following symptom onset in 112 women with NMOSD. The ARR in the first-trimester postpartum period (1.44 ± 2.04) was higher than that before pregnancy (0.23 ± 0.48; p < 0.001) and during pregnancy. The EDSS score increased from 1.40 ± 1.38 before pregnancy to 1.99 ± 1.78 postpartum (p = 0.004). Multivariate Cox proportional hazards models indicated that increased disease activity 1 year before conception (HR = 1.79, 95% CI 1.09–2.92, p = 0.021) and lack of immunotherapy during pregnancy and the postpartum period (HR = 5.25, 95% CI 1.91–14.42, p = 0.001) were independent risk factors that predicted pregnancy-related attacks. Interpretation: The postpartum period is a particularly high-risk time for the onset and relapse of NMOSD. Pregnancy exerted detrimental effects on the disease courses of NMOSD. Immunotherapy during pregnancy and the postpartum period might be recommended to decrease the risk of pregnancy-related attacks. Larger-scale prospective studies are warranted to confirm our findings.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare demyelinating disease of the central nervous system characterized by recurrent optic neuritis and longitudinally extensive transverse myelitis. It is generally appreciated that pregnancy plays a modulatory role in the course of autoimmune diseases. During pregnancy, the increase in progesterone and estrogen levels is associated with the progressive transformation from the Th1- to Th2-mediated immune responses, which might aggravate the disease course of NMOSD. NMOSD is a disorder that affects mainly women in their childbearing years, and its activity may be influenced by the cytokines secreted during pregnancy. Aquaporin-4 (AQP4) is strongly expressed in human placental syncytiotrophoblasts, and experimental studies have shown that it is correlated with AQP4-mediated placental inflammation and fetal death in rats. Hence, determining whether pregnancy affects the disease courses of NMOSD, and vice versa, is significant. Previous studies have demonstrated that the annualized relapse rate (ARR) of NMOSD is significantly increased during the first 3 months of the postpartum period, while the ARR during pregnancy usually does not change. However, information regarding the predictors of pregnancy-related attacks in patients with NMOSD is still scarce.
The aim of the present study was to assess the impact of pregnancy on the courses of NMOSD and the independent risk factors for pregnancy-related attacks.

Methods

Participants

All of the participants in the study were from the West China Hospital, Sichuan University between September 2009 and September 2020. Patients enrolled between 2009 and 2016 met the Wingerchuk 2006 criteria for neuromyelitis optica, and patients enrolled after 2016 met the revised Wingerchuk 2015 criteria for NMOSD. This study was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University, and informed consent was provided by each participant before enrollment.

Measures

The data for this retrospective study were obtained from our NMOSD database, and the following data were collected: demographic data, age at onset, disease duration, history of attacks, ARR (the number of attacks per patient-year), Expand Disability Status Scale (EDSS) scores 1 year before and after pregnancy, AQP4-Ab serostatus (cell-based assay, CBA), coexisting autoimmune disorders, therapeutic regimens (agents, maintenance time, and dosages), and information on obstetric data (including the number of pregnancies, fetal outcomes of each pregnancy, and methods of delivery). Patients with no immunotherapies (NIT) were those who have not received treatment or were treated with only symptomatic treatment or traditional Chinese drugs.

Pregnancies that occurred after the onset of NMOSD and those in which the disease occurred during the pregnancy or within 1 year after delivery or abortion were defined as informative. The pregnancy-related attack was defined as an attack that occurred during pregnancy or within 1 year of delivery/abortion. The pregnancy-related attack was defined as informative. The pregnancy-related attack was defined as a loss of intrauterine pregnancy during the first 24 weeks. A relapse was defined as a new worsening neurological function lasting more than 24 h in the absence of other identifiable causes and occurring more than 30 days after a previous attack. A severe attack was defined as acute myelitis with an EDSS score of $\geq 6.0$ (unilateral/bilateral assistance needed to walk, wheelchair dependency, restriction to a bed, or even death) or an increase of $\geq 0.5$ points if the patient had a baseline EDSS score $\geq 6.0$. In cases of ON, a severe attack was defined as visual acuity $\leq 0.1$ or worse. An increase in EDSS score was defined as at least 0.5 points 1 year after delivery compared with 1 year before pregnancy.

Statistical analysis

Quantitative data are described as the median (range) or mean ± standard deviation. The mean ARR for each period was compared with the ARR during the 12–0 months before pregnancy using one-way repeated measurement ANOVA. Univariate Cox proportional hazards model was performed to assess the association between maternal variables and whether pregnancy-related attacks occurred. Covariates, including maternal age at delivery/abortion, AQP4-Ab serostatus, increased disease activity 1 year before conception (at least an attack 1 year before conception), NIT during pregnancy and the postpartum period, NIT 1 year before conception, and the occurrence of other autoimmune disorders, were evaluated by univariate Cox analysis, and those with a cutoff of $p < 0.1$ were further included in the multivariate Cox analysis to determine independent risk factors for pregnancy-related attacks in patients with NMOSD. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the risk of predictors. All statistical analyses were conducted using SPSS v. 25.0 software (IBM Corp., Armonk, NY, USA). The level of significance was defined by a 2-tailed $p$ value of $<0.05$ for multivariate Cox regression analysis.

Results

Demographic and disease-related characteristics

From September 2009 to September 2020, we retrospectively enrolled 568 female patients with NMOSD in the Department of Neurology, West China Hospital, Sichuan University. Among the 568 enrolled patients, there were 202 informative pregnancies in 112 patients, 91.9% of whom were seropositive for AQP4 antibodies. The median age at onset was 25.1 years, and 26.8% of patients were complicated by other autoimmune diseases. A total of 72.3% of patients were treated with immunosuppressants in remission. An overview of the included patients is presented in Figure 1.
Pregnancy-related characteristics and complications

Of these 112 patients, 46 (41.1%) developed the first manifestations of NMOSD either during pregnancy or within 1 year after delivery or abortion. Among these 46 patients, the onset of NMOSD occurred during pregnancy in 11 patients and within 1 year after delivery or abortion (27 and 8 patients, respectively) in 35 patients. Eighty-one patients experienced 155 pregnancies after the onset of NMOSD, of which 75 pregnancies (45 deliveries and 30 abortions) from 53 patients had pregnancy-related attacks. Of these 155 pregnancies in the group with the previous NMOSD, 80 (51.6%) resulted in abortion (74 elective abortions and 6 spontaneous abortions), and 75 resulted in births to infants. Of the 75 deliveries following symptom onset that resulted in a live birth, 10 (13.3%) were preterm deliveries in the third trimester. The frequency of cesarean sections was 37.3% (28/75). There were no neonatal malformations or stillbirths. The characteristics of the 75 deliveries are summarized in Table 1.

Altogether, there were 95 abortions in the entire cohort. The reasons for abortions were attacks related to NMOSD during pregnancy (n = 9), unplanned pregnancy (n = 57), fear of drug-affected fetuses (n = 15), ectopic pregnancies (n = 4), spontaneous abortion (n = 6), embryo malformation (n = 3), and hydatidiform mole (n = 1) (Table 2).

Risk of relapse related to pregnancy

During the 1 year before pregnancy, among 58 patients who had successful pregnancies, relapses occurred in 15 of the 75 pregnancies (20.0%), whereas 9 (12.0%) and 42 (56.0%) of 75 pregnancies were associated with relapses during pregnancy and 1 year after pregnancy, respectively. Regarding the 52 relapses that occurred within 1 year after delivery, the median interval between delivery and relapse was 3.0 (0.03–11.43) months. Among 30 deliveries (40.0%), there were no relapses during pregnancy or 1 year after pregnancy.

Among 58 patients who had successful pregnancies, there were 64 relapses during pregnancy and the postpartum period, including 29 severe attacks. Regarding the 64 relapses, the median EDSS score was 3.0 (range 0–9.0), and for the 29 severe attacks, the median EDSS score was 8.0 (range 3.0–9.0).

The mean ARR of each period of the 75 successful pregnancies after disease onset is shown in Figure 2. The ARR during pregnancy did not differ from that before pregnancy, but it increased significantly during the first trimesters after delivery (1.44 ± 2.04 vs. 0.23 ± 0.48,
The mean EDSS score was 1.40 ± 1.38 before delivery and increased to 1.99 ± 1.78 1 year after
delivery (p = 0.004). A total of 34.7% (26/75) of pregnancies were
associated with increased EDSS scores compared with
prepregnancy scores.

### Treatment before, during, and after pregnancy
Among 155 pregnancies after the onset of NMOSD,
20.6% (32/155) received immunotherapy 1 year before
pregnancy, including oral glucocorticoids (n = 5), oral
tacrolimus (n = 2), oral glucocorticoids plus azathioprine
(AZA) (n = 16), and oral glucocorticoids plus myco-
phenolate mofetil (MMF) (n = 9). Four (one received oral
glucocorticoids, three received oral glucocorticoids plus
AZA) stopped immunotherapy during pregnancy because
patients worried about the possible side effects on the
fetus. A total of 18.1% (28/155) of pregnancies received
immunotherapy during pregnancy and the postpartum
period, including oral glucocorticoids (n = 4), oral tacro-
limus (n = 2), oral glucocorticoids plus AZA (n = 13),
and oral glucocorticoids plus MMF (n = 9, all had a
selective abortion for fear of drug-affected fetuses). Of
these 28 pregnancies, there were eight successful deliver-
ies, and all eight infants were healthy from birth to early
childhood. Seven pregnancies received oral glucocorti-
coids plus AZA, and one pregnancy received glucocorti-
coids during pregnancy and the postpartum period. The
other 20 pregnancies ended with abortion, including 18
cases of elective abortion and two cases of spontaneous
abortion. Among the 18 cases of elective abortion, 11
cases were worried about drug side effects (nine cases of
MMF and two cases of tacrolimus), and seven cases were
unplanned pregnancies (four cases of AZA plus glucocor-
ticoids and three cases of glucocorticoids). The two cases
of spontaneous abortion received AZA during pregnancy
and postpartum.

The daily dosage of MMF for each patient was 1000–
1500 mg/day, and AZA was started at 25 or 50 mg daily

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Table 1. Characteristics of NMOSD patients who experienced pregnancy after disease onset.

| Characteristics                  | Successful pregnancy | Elective abortion | Spontaneous abortion |
|----------------------------------|----------------------|-------------------|----------------------|
| Participants, n                  | 58                   | 49                | 6                    |
| Times of deliveries/abortions, n | 75                   | 74                | 6                    |
| Age at onset, years, mean ± SD (range) | 22.0 ± 5.3 (13.1–39.6) | 25.3 ± 8.2 (13.1–41.3) | 23.3 ± 6.0 (13.5–29.4) |
| Age at delivery/abortion, mean ± SD (range) | 28.3 ± 4.9 (18.7–43.5) | 30.4 ± 8.2 (19.1–44.4) | 29.4 ± 6.5 (13.1–41.3) |
| Vaginal delivery: cesarean section | 47:28                |                   |                      |
| Breastfeeding more than 2 months, n (%) | 59 (78.7)           |                   |                      |
| Treatment during pregnancy, n (%) | 8 (10.7)             | 20(27.0)          | 3(50.0)              |
| Azathioprine with glucocorticoids | 7                    | 6                 | 2                    |
| Mycophenolate mofetil            | 0                    | 9                 | 1                    |
| Glucocorticoids                  | 1                    | 5                 | 0                    |
| No immunotherapy, n (%)          | 67 (89.3)            | 54(73.0)          | 3(50.0)              |

NMOSD, neuromyelitis optica spectrum disorder; n, number; SD, standard deviation.

Table 2. Causes of abortion among the NMOSD patients with informative pregnancies in our study.

| Causes of abortion                      | Total (95) |
|-----------------------------------------|------------|
| Unplanned pregnancy                     | 57 (60)    |
| Fear of drug-affected fetuses           | 15 (15.8)  |
| NMOSD attack during pregnancy           | 9 (9.5)    |
| Spontaneous abortion                    | 6 (6.3)    |
| Ectopic pregnancies                     | 4 (4.2)    |
| Embryo malformation                     | 3 (3.2)    |
| Hydatidiform mole                       | 1 (1.0)    |

NMOSD, neuromyelitis optica spectrum disorder; n, number.
and was increased 2 weeks later to 2–3 mg/kg based on body weight. Other immunosuppressants included tacrolimus. Some patients received low doses of corticosteroids (5–10 mg/day of prednisone) as a single therapy to prevent relapses.

**Analyses of predictors of pregnancy-related attacks in patients with NMOSD**

Among 155 pregnancies after the onset of NMOSD, 75 pregnancies with pregnancy-related attacks and 80 pregnancies without pregnancy-related attacks were included in the analyses of risk factors, and Cox regression analysis was used to explore the potentially related predictors. The univariate Cox regression analysis indicated that age at delivery/abortion (<32 years old), increased disease activity 1 year before conception, NIT 1 year before conception, and NIT during the pregnancy and postpartum periods were associated with an increased risk of pregnancy-related attacks in NMOSD (Table 3). We observed no association between the risk of pregnancy-related attacks and concomitant autoimmune diseases or AQP4-Ab serostatus. Subsequently, multivariate Cox regression analysis further confirmed that patients who did not receive immunotherapy during pregnancy and the postpartum period (HR = 8.92, 95% CI 1.61–49.42, \( p = 0.012 \)) had a higher risk of pregnancy-related attacks.

**Discussion**

We described the demographic, clinical, and pregnancy-related characteristics of 112 informative patients with NMOSD in a Chinese population. We found the ARR in the first trimester postpartum period was significantly higher than that before pregnancy and during pregnancy. The EDSS score increased 1 year after delivery than before pregnancy, and multivariate Cox regression analysis indicated that lack of immunotherapy during pregnancy and the postpartum period was an independent risk factor that predicted pregnancy-related attacks.

Pregnancy evokes notable changes in the immunological and hormonal milieu that are essential to sustaining a successful pregnancy. NMOSD are autoimmune disorders that are mediated by humoral immunity as the main mechanism. Pregnancy seems to be associated with a shift from cell-mediated immunity toward humoral immunity. Thus, it was generally inferred that pregnancy may negatively influence the disease course. The present study indicated that many of the enrolled NMOSD patients who were pregnant experienced a pregnancy-related attack (either an onset event or relapse). NMOSD is relatively more common in China than in Western countries. Considering that many female patients with NMOSD are in their childbearing years, the high percentage of pregnancy-related attacks suggests that a therapeutic strategy for female patients with NMOSD is needed.

In our study, the impact of pregnancy on the course of NMOSD was marked by a measurable increase in the relapse rate after delivery or abortion, whereas the relapse rate did not change significantly during gestation. We also found that delivery or abortion may significantly induce disease onset. Approximately 60% (45/75) of successful pregnancies were correlated with postpartum relapses; additionally, 46 patients developed the disease either during pregnancy or within 1 year after delivery/abortion. Shimizu et al. and Huang et al. found that 23.4% (11/47) and 20.2% (33/163) of women with NMOSD, respectively, had disease onset after pregnancy or childbirth. Whether pregnancy or childbirth is a vital triggering factor for disease onset is uncertain. Additionally, consistent with previous reports,11–18,21 our study confirmed a trend in the rebound of the relapse of NMOSD within the first-trimester postpartum period. Fragoso et al. and Tong et al. also respectively observed an increased risk of relapse in the second and third-trimester postpartum period.11,21 Regarding the significant worsening of EDSS scores following pregnancy, the result was consistent with

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**Table 3. Predictors of pregnancy-related attacks in NMOSD according to univariate and multivariate Cox proportional hazards models.**

|                         | Univariate analysis | Multivariable analysis |
|-------------------------|---------------------|------------------------|
|                         | HR (95% CI)         | \( p \)-values         | HR (95% CI)         | \( p \)-values         |
| Age at delivery/abortion (<32 years old) | 1.61 (0.92–2.84) | 0.098  | 0.397          |
| AQP4-Ab serostatus, positive     | 1.06 (0.51–2.20)   | 0.887     | 0.787          |
| Increased disease activity 1 year before conception | 1.62 (0.99–2.64) | 0.054  | 1.79 (1.09–2.92) | 0.021*      |
| Autoimmune comorbidity         | 1.18 (0.61–2.30)   | 0.629     | 0.787          |
| No immunotherapy 1 year before conception | 2.93 (1.35–6.38) | 0.007  | 5.25 (1.91–14.42) | 0.001*      |
| No immunotherapy during pregnancy and postpartum | 4.92 (1.80–13.49) | 0.002  | 5.25 (1.91–14.42) | 0.001*      |

CI, confidence interval; HR, hazard ratio; NMOSD, neuromyelitis optica spectrum disorder.

\*\( p \)-value <0.05 by multivariable Cox proportional hazards models.

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AQP4-Ab-positive individuals with NMOSD have coexistence with coexisting autoimmune disorders, and up to 25% of women with NMOSD may also be influenced by pregnancy-related attacks, and the result was supported by another previous study.\textsuperscript{14} Kim et al.\textsuperscript{12} and Klawiter et al.\textsuperscript{19} proposed that pregnancy was a risk factor for relapse and disability in patients with NMOSD.

Moreover, 7.5% (6/80) of the miscarriage rate in our study was observed in NMOSD patients with pregnancy after disease onset, which was consistent with previous studies. A miscarriage rate of 5.8%, 10%, and 12.9% was reported by a Brazilian study,\textsuperscript{11} a Mexican study,\textsuperscript{22} and an international cohort,\textsuperscript{25} respectively. Miscarriage in patients with NMOSD may be explained by the following: AQP4, the main target antigen in NMOSD, is ubiquitously expressed in the healthy placenta, and levels are highest mid-gestation;\textsuperscript{9} consequently, women with active NMOSD have a high risk of miscarriage. Pregnancy outcomes of females with NMOSD may also be influenced by coexisting autoimmune disorders, and up to 25% of AQP4-Ab-positive individuals with NMOSD have coexisting autoimmune disorders.\textsuperscript{24} Furthermore, some of the immunosuppressive therapies currently for patients with NMOSD could pose substantial risks to the developing fetus.\textsuperscript{25–27} Of note, Kim et al.\textsuperscript{12} and Klawiter et al.\textsuperscript{19} observed a large number of elective abortions in patients with NMOSD, and a large proportion of patients had avoided or delayed pregnancy, respectively. These findings might reflect the concerns of patients and doctors about the suitability and safety of immunotherapies during pregnancy.

Most of the patients with successful pregnancies had relatively low prepregnancy disease activity, and the significant increase in the number of relapses related to delivery is noteworthy. We observed a correlation between the ARR before pregnancy and that during and after pregnancy, indicating that the risk of relapse after delivery is high in patients with high prepregnancy disease activity. Likewise, the risk of relapse also had a tendency to increase during the third and fourth trimesters postnatal period. These results demonstrated that the influence of delivery on NMOSD may be detrimental.

Our multivariate Cox proportional hazards models suggested that patients with NIT during the pregnancy and postpartum periods had a higher risk of pregnancy-related attacks, and the result was supported by another previous study.\textsuperscript{14} Kim et al. found that the risk of relapse was also higher during the 6–12 months postpartum period when patients did not receive immunotherapy.\textsuperscript{12} Shimizu et al. proposed that ARR was higher in patients with NMOSD receiving no or low-dose immunosuppressive therapy during pregnancy than in those who continued appropriate immunosuppressive treatment.\textsuperscript{14} Kim et al. indicated that pregnancy-related attack was negatively associated with pregnancy after the initiation of rituximab.\textsuperscript{28} A recently published study found that taking immunosuppressive therapy just before or during pregnancy reduces the risk of relapses in patients with NMOSD.\textsuperscript{29} These findings indicate that sufficient immunosuppressive therapy can prevent relapses of NMOSD postpartum. Therefore, maintenance treatment or starting immunotherapy immediately after delivery might be recommended. In addition, our study found patients with increased disease activity 1 year before conception had a higher risk of pregnancy-related attacks, which also indicated that it is necessary to start immunotherapy before pregnancy to reduce disease activity. In our study, most females stopped immunotherapy 1 year before pregnancy due to upcoming pregnancy for fear of possible side effects of immunotherapy on the fetus, therefore, only 20.6% of patients received immunotherapy the 1 year before pregnancy.

According to a previous study, administration of tacrolimus during pregnancy was not correlated with congenital malformations.\textsuperscript{30} A systematic review and meta-analysis of the impacts of treatment with azathioprine during pregnancy showed that there was no significant association between azathioprine and congenital defects or low birth weight.\textsuperscript{31} In our study, neither congenital malformation nor abnormal complications were observed in patients who received immunotherapy during pregnancy, which may also be partly attributed to the small sample size. The high abortion rate among informative pregnancies should also be noted. Of these pregnancies, 48% ended in abortion, though the vast majority were elective. The absence of definitive evidence based on guidelines seemed to be the main reason for the high rate of abortions. To date, guidelines for immunotherapy for pregnant females with NMOSD have not been established. Considering the relatively small sample size of patients who received immunotherapy during pregnancy, the safety of immunosuppressive therapy for pregnant females with NMOSD needs to be confirmed by larger, prospective studies in the future.

It is remarkable that pregnancy seems to negatively affect the course of NMOSD in all populations. Hence, planning adequate postpartum management in consideration of the increased risk of postpartum relapse is crucial. Nevertheless, our study had several limitations. First, the nature of the retrospective study from a single center introduces potential selection bias. Second, most patients in our center were not treated with immunotherapy during pregnancy and postpartum for fear of the possible adverse effects of immunotherapy on the fetus, presumably resulting in a low treatment rate among the detected cases and thus relatively small samples (attributed to also the rarity of the disease). Additional studies with longer follow-ups and larger sample sizes are, therefore, warranted to confirm our findings.
Conclusions

In conclusion, there is a propensity toward relapse or disease onset during the first trimester postpartum in NMOSD and pregnancy may aggravate patients' disability. Immunotherapy during pregnancy and the postpartum period may reduce the risk of relapse.

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Author Contributions

H.Z. contributed to the conception and design of the study; H.C., Z.S., Y.Z., Y. Q., Y.L., and L.K. contributed to the acquisition and analysis of the data. Q.D. contributed to drafting the text and preparing the tables and figures.

Conflict of Interest

Nothing to report.

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