Original research

Neuromyelitis optica spectrum disorder: pregnancy-related attack and predictive risk factors

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ABSTRACT

Objectives To investigate the influence of pregnancy on patients with neuromyelitis optica spectrum disorder (NMOSD) and to identify risk factors that predict pregnancy-related attack.

Methods From January 2015 to April 2019, 418 female patients with NMOSD were registered at Huashan Hospital. We retrospectively reviewed their medical records and identified 110 patients with 136 informative pregnancies, of whom 83 were aquaporin-4 antibody (AQP4-ab) positive and 21 were myelin oligodendrocyte glycoprotein-antibody-positive. Pregnancy-related attack was defined as an attack that occurred during pregnancy or within 1 year after delivery/abortion. We compared annualised relapse rate (ARR) during 12 months before pregnancy with that during every trimester of pregnancy and after delivery/abortion. Multivariate analyses were used to explore the independent risk factors involved and a nomogram was generated for the prediction of pregnancy-related attack. Thirty-five female patients from 3 other centres formed an external cohort to validate this nomogram.

Results ARR increased significantly during the first trimester after delivery (p<0.001) or abortion (p=0.019) compared with that before pregnancy. Independent risk factors predicting pregnancy-related attack included age at delivery/abortion (20–26.5, p=0.018; 26.5–33, p=0.001), AQP4-ab titre (≥1:100, p=0.049) and inadequate treatment during pregnancy and postpartum period (p=0.004). The concordance index of nomogram was 0.87 and 0.77 using bootstrap resampling in internal and external validation.

Conclusions The first trimester post partum is a high-risk period for NMOSD recurrence. Patients with younger age, higher AQP4-ab titre and inadequate treatment are at higher risk for pregnancy-related attack.

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) reflect categories of auto-antibody-induced inflammatory diseases of the central nervous system (CNS)—predominantly involving optic nerves, spinal cord, and brainstem—leading to blindness and paralysis.1 The presence of pathogenic aquaporin-4 antibody (AQP4-ab) in serum is highly specific for NMOSD and found in most patients with NMOSD.2 Serum myelin oligodendrocyte glycoprotein antibody (MOG-ab) has also been recently detected in a portion of patients with AQP4-ab-negative NMOSD.3

NMOSD principally affects women, many of whom develop active disease during childbearing years. Clinical and experimental studies have illustrated that AQP4 is expressed on human and animal placenta, and have associated AQP4-mediated placental inflammation with fetal death.4 5 Unlike MS, a lack of reduction in relapses during pregnancy is observed in NMOSD.6 7 Previous studies have demonstrated that the annualised relapse rate (ARR) of patients with NMOSD increased specifically during the first 3 months post partum,6 8 correlating with high rates of miscarriage.9 Consequentially, disability worsening during and after pregnancy has been reported.6 11–14 NMOSD is considered to be the most common type of CNS inflammatory demyelinating disease in China, whereas multiple sclerosis (MS) is relatively rare. However, information regarding pregnancy-related attack in Chinese patients with NMOSD is still lacking.

In the present study, we aimed to investigate the influence of pregnancy on Chinese patients with NMOSD and to identify independent risk factors that predict pregnancy-related attack.

METHODS

Cohort and data collection

This is a retrospective data collection study. From January 2015 to April 2019, 688 consecutive patients with NMOSD were registered and followed up at Shanghai Huashan Hospital. Among them, 418 patients were female and their medical records were retrospectively reviewed. Altogether, 110 female patients with 136 pregnancies were collected and included in the study (figure 1). The inclusion criteria were: (1) female; (2) fulfil the diagnostic criteria of NMOSD established by the International Panel in 2015;1 3 with informative pregnancies.

The demographics and clinical data of the 110 female patients with informative pregnancies were collected. Among them, there were 76 pregnancies conceived after disease onset of 60 patients and 60 pregnancies of 60 patients with disease onset during pregnancy or within 1 year after delivery/abortion. Relapses were defined as new or worsening neurological symptoms lasting longer than 24 hours without other aetiology. Pregnancy-related attack was defined as an attack that occurred during pregnancy or within 1 year of delivery/abortion.2 Pregnancy complications and outcomes were collected.
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For patients exhibiting pregnancy-related attacks after disease onset, the number of attacks was recorded during 12–0 months before pregnancy (BP); during the first (DP1), second (DP2) and third (DP3) trimesters of pregnancy and during 0–3 (PP1), 4–6 (PP2) and 7–12 months (PP3+4) after delivery/abortion. We compared the ARR and Expanded Disability Status Scale (EDSS) score during the baseline period of 12 months before pregnancy with that during every trimester of pregnancy and after delivery/abortion.

To identify the risk factors for pregnancy-related attacks, 60 patients with 76 pregnancies after disease onset from Huashan Hospital were included in analysis as the primary cohort. To further verify the discrimination of the risk factors, 35 female patients with 44 pregnancies after disease onset from the Third Affiliated Hospital of Sun Yat-sen University (n=31), Sir Run Run Shaw Hospital (n=7) and the First Affiliated Hospital of Wenzhou Medical University (n=6) were included as the external validation cohort.

All patients at Huashan Hospital and patients in the validation cohort from other three centres had undergone serum AQP4-ab and MOG-ab detection using the same fixed cell-based indirect immune-fluorescence test as part of a routine diagnostic approach. HEK293 cells transfected with either full-length human MOG or the M1 isoform of AQP4 were employed.

Statistical analysis

We performed statistical analyses with SPSS V.22.0 (SPSS, Chicago, Illinois, USA), and the figures were generated with GraphPad Prism 6 (GraphPad Software, La Jolla, California, USA). Continuous variables were expressed as means±1 SD or medians with ranges. The χ² or Fisher’s exact test was used to compare the discrete variables, while a Student’s t-test or Mann-Whitney U test was employed to compare the quantitative data of the AQP4 and MOG cohort. A paired t-test or Wilcoxon signed-rank test was used to compare ARR and EDSS score during each pregnancy-related period with those before pregnancy, and participants with NMOSD served as their own controls for this comparison.

The association between maternal variables and counts of pregnancy-related attacks was evaluated using univariate Poisson regression, while the association between maternal variables and whether pregnancy-related attacks occurred was determined using univariate logistic regression. Based on clinical reasoning or previous reports,7–9 13 15 variables that were possible to associate with pregnancy-related attack were selected, including age at disease onset, age at delivery/abortion, time interval from disease onset to pregnancy, time interval from last attack to pregnancy, treatment during pregnancy and after delivery/abortion, AQP4-ab titre, relapse within 1 year before pregnancy, ARR before pregnancy, EDSS score before pregnancy and concomitant auto-antibodies. Variables related to a significant change (p<0.1) in the OR defined by univariate analysis were further analysed using multivariate Poisson or logistic regression.

Treatments during pregnancy and after delivery/abortion were classified as inadequate and adequate treatment. Inadequate treatment referred to (1) no treatment at all, (2) usage of low-dose oral prednisone (≤10 mg/day) as single therapy. Adequate treatment was defined as (1) usage of relatively higher dose oral prednisone (>10 mg/day), (2) usage of immunosuppressant (azathioprine 100 mg/day or tacrolimus 3 mg/day) combined with or without oral steroid, (3) a dose of rituximab (375 mg/m²) within 6 months before conception and shortly after delivery.

The first available AQP4-ab titre which was detected in a remission status was included in the univariate and multivariate analysis of potential risk factors.

We enhanced the predictive model of pregnancy-related attack with risk factors depicted in a nomogram using the rms package in R, V.3.6.2 (http://www.r-project.org/).16 Nomogram was generated according to the probability of the occurrence of pregnancy-related attack using multivariate logistic regression in the primary cohort and further validated in the external cohort. We employed the Concordance index (C-index) to then measure

Figure 1  Informative pregnancies from 110 female patients with NMOSD. N, number of pregnancies; NMOSD, neuromyelitis optica spectrum disorder.
had pregnancy-related attacks, with 31 patients having undergone 31 deliveries and 18 patients who underwent 19 abortions. Twenty-six pregnancies from 22 patients had no pregnancy-related attacks, with 12 patients underwent 12 deliveries and 13 patients underwent 14 abortions (figure 1).

**The pregnancy-related characteristics of patients with different antibody subsets**

The pregnancy-related characteristics of patients with AQP4-ab and MOG-ab are shown in table 1. There were 83 AQP4-ab-positive patients who experienced 108 informative pregnancies, with 126 pregnancy-related attacks, and their median AQP4-ab titre was 1:32 (range, 1:10–1:3200). Of these, the attacks during the 0–3 months after delivery-abortion were the most common, with 51 counts (40.5%). The pregnancy outcomes included 60 term deliveries, 5 premature deliveries, 39 elective abortions, 4 spontaneous abortions and 3 neonatal malformations—including undevolved external ear, dacrocytob obstruction and scoliosis. We observed no pre-eclampsia during pregnancy. Of the 50 AQP4-ab-positive patients who underwent 66 pregnancies after disease onset, the mean adjusted ARR was 0.33 (95% CI 0.26 to

### Table 1 The pregnancy-related characteristics of patients with NMOSD with AQP4-ab and MOG-ab

|  | AQP4 cohort | MOG cohort |
|---|---|---|
| Number of patients/number of patients with pregnancies after disease onset | 83/50 | 21/5 |
| Number of informative pregnancies/number of pregnancies after disease onset | 108/66 | 28/4.6 |
| Number of total pregnancy-related attacks | 126 | 28 |
| Age at disease onset, year, mean±SD | 25.8±6.3 | 26.7±5.9 |
| Age at delivery-abortion, year, mean±SD | 28.4±4.6 | 28.3±4.6 |
| AQP4-ab or MOG-ab titre, median (range) | 1:32 (1:10–1:3200) | 1:32 (1:10–1:3200) |
| Number of pregnancy-related attacks (%) | | |
| DP1 | 13 (10.3) | 2 (7.1) |
| DP2 | 9 (7.1) | 1 (3.6) |
| DP3 | 4 (3.2) | 0 (0) |
| PP1 | 51 (40.6) | 11 (39.3) |
| PP2 | 25 (19.8) | 5 (17.9) |
| PP3+4 | 24 (19.0) | 9 (32.1) |
| Number of different pregnancy outcomes or complications (%) | | |
| Term delivery | 60 (55.6) | 18 (85.7) |
| Premature delivery | 5 (4.6) | 1 (4.8) |
| Elective abortion | 39 (36.1) | 2 (9.5) |
| Spontaneous abortion | 4 (3.7) | 0 (0) |
| Neonatal malformation | 3 (2.8) | 0 (0) |
| Pre-eclampsia | 0 (0) | 0 (0) |
| BP-ARR mean (95% CI) | 0.33 (0.19 to 0.47) | 0.40 (0.26 to 0.54) |
| Adjusted BP-ARR* mean (95% CI) | 0.33 (0.26 to 0.41) | – |
| PP-ARR mean (95% CI) | 0.65 (0.46 to 0.84) | 0.60 (0.38 to 0.82) |
| Adjusted PP-ARR* mean (95% CI) | 0.69 (0.61 to 0.78) | – |

*ARR was adjusted using a Poisson regression for treatment variables (inadequate or adequate treatment) during 12–0 months pre-pregnancy and during 0–12 months after delivery/abortion.

### Table 2 The demographics and clinical characteristics of patients with NMOSD with pregnancies after disease onset

|  | Primary cohort | Validation cohort |
|---|---|---|
| Number of patients | 60 | 35 |
| Number of AQP4-ab/MOG-ab positivity | 50/5 | 33/2 |
| Number of pregnancies after disease onset | 76 | 44 |
| Time interval from disease onset to first relapse, m, median (range) | 15.0 (0–231.0) | 12.0 (0–108.0) |
| Age at disease onset, year, mean±SD | 23.8±6.3 | 23.5±5.4 |
| Age at delivery/abortion, year, mean±SD | 28.7±4.4 | 29.6±4.2 |
| Total number of pregnancy-related attacks | 69 | 44 |
| Type of pregnancy-related attack, n (%) | | |
| Optic neuritis | 31 (44.9) | 19 (45.5) |
| Acute myelitis | 35 (50.7) | 28 (63.6) |
| Area postrema syndrome | 4 (5.8) | 2 (4.5) |
| Acute brainstem syndrome | 4 (5.8) | 0 (0) |
| Comitantautanto-autoantibodies, n (%) | 26 (42.3) | 15 (42.9) |
| ANA | 22 (36.7) | 14 (40.0) |
| DNA-ab | 12 (20.0) | 5 (14.3) |
| dsDNA-ab | 1 (1.7) | 2 (5.7) |
| ANCA | 0 (0) | 0 (0) |
| ACA | 1 (1.7) | 0 (0) |
| TPO-ab and TG-ab | 13 (21.7) | 1 (2.9) |
| Treatment variables, n (%) | | |
| Adequate treatment* | 10 (13.2) | 13 (29.5) |
| Inadequate treatment† | 56 (86.8) | 31 (70.5) |

* Adequate treatment was defined as (1) usage of relatively higher dose oral prednisone (>10 mg/day), (2) usage of immunosuppressant (azathioprine 100 mg/day or tacrolimus 3 mg/day) combined with or without oral steroid, (3) a dose of rituximab (375 mg/m²) within 6 months before conception and shortly after delivery.

†Inadequate treatment referred to (1) no treatment at all, (2) usage of low-dose oral prednisone (≤10 mg/day) as single therapy.
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0.41) during 12–0 months before pregnancy and 0.69 (95% CI 0.61 to 0.78) during 0–12 months after pregnancy.

There were 21 MOG-ab-positive patients experiencing 21 informative pregnancies, with 28 pregnancy-related attacks. Of these, the attacks during the first trimester post partum were also the most common, with 11 counts (39.3%). The pregnancy outcomes of the MOG subgroup included 18 term deliveries, 1 premature delivery and 2 elective abortions; no spontaneous abortion, neonatal malformations or pre-eclampsia were observed. The pregnancy outcomes of the remaining six seronegative patients were six term deliveries and one elective abortion.

Altogether there were 42 elective and 4 spontaneous abortions of the entire cohort. The reasons for elective abortions were NMOSD attack during pregnancy (n=14), unplanned pregnancy (n=13), concern over medication side effects (n=8), embryonic demise (n=3), abnormal prenatal screening (n=2), advanced age considered not appropriate for delivery (n=1), and poor physical condition (n=1). Spontaneous abortions were only seen in AQP4-ab-positive patients, and were considered to be induced by over fatigue (n=3) or of unknown reason (n=1).

ARR and EDSS score in each phase of pregnancies after disease onset

The demographics and clinical characteristics of patients with NMOSD who underwent pregnancies after disease onset in the primary and validation cohort are listed in table 2. The mean ARR and EDSS scores of each period from the 31 deliveries and 19 abortions in the primary cohort are shown in figure 2A–D. In the delivery group, ARR arose significantly during the first and second trimesters post partum compared with prepregnancy period (p<0.001 and p=0.015, respectively), while the ARR during other phases did not differ. The EDSS score increased significantly during pregnancy and within 1 year after delivery compared with that before pregnancy (p=0.004 and p<0.001, respectively). The ARR increased significantly during pregnancy and the first trimester after abortion compared with that before pregnancy (p=0.008 and p=0.019, respectively). Similarly, the EDSS score increased significantly during pregnancy and within 1 year after abortion compared with that before pregnancy (p=0.016 and p<0.001, respectively).

Risk factors and the prediction model of pregnancy-related attack

Fifty pregnancies with pregnancy-related attacks and 26 pregnancies without pregnancy-related attacks were included in the analyses of risk factors. Using univariate Poisson regression (table 3), we identified increased age at disease onset as being associated with a decreased OR for counts of pregnancy-related attacks (p=0.045); and age (20–26.5, 26.5–33) at delivery/abortion, inadequate treatment during pregnancy and after delivery-abortion, and high AQP4-ab titre (≥1:100) were associated with an increased OR of counts of pregnancy-related attacks (p=0.008, 0.009, 0.011 and 0.004, respectively). We observed no association between counts of pregnancy-related attacks and time interval from disease onset to pregnancy, time interval from last attack to pregnancy, relapse within 1 year before pregnancy, ARR before pregnancy, EDSS score before pregnancy or counts (≥1, ≥2) of concomitant autoimmune antibodies. Using multivariate Poisson regression, we further defined that age (20–26.5, 26.5–33) at delivery/abortion, inadequate treatment during...
pregnancy and after delivery-abortion and high AQP4-ab titre (≥1:100) were independently associated with an increased OR of counts of pregnancy-related attacks (p=0.028, 0.016, 0.014 and 0.036, respectively).

Using univariate logistic regression (table 4), we identified increased age at disease onset as being associated with a decreased OR of the occurrence of pregnancy-related attacks (p=0.027). Age (20–26.5, 26.5–33) at delivery-abortion, inadequate treatment during pregnancy and after delivery-abortion and high AQP4-ab titre (≥1:100) were also associated with an increased OR of the occurrence of pregnancy-related attacks (p=0.002, 0.001, 0.005 and 0.008, respectively). Multivariable logistic regression further demonstrated that age (20–26.5, 26.5–33) at delivery-abortion, inadequate treatment during pregnancy and after delivery-abortion and high AQP4-ab titre (≥1:100) were independently associated with an increased OR of the occurrence of pregnancy-related attacks (p=0.018, 0.001, 0.004 and 0.049, respectively).

We further created a predictive model for pregnancy-related attacks using a nomogram according to whether pregnancy-related attacks (≥1:100) were also associated with an increased OR of counts of pregnancy-related attacks (p=0.028, 0.016, 0.014 and 0.036, respectively).

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the AQP4 cohort (2, 0–9) and the MOG cohort (1, 0–7.5) (p=0.003).

**DISCUSSION**

Through a series of studies, investigators had explored the effect of pregnancy on the frequency of NMOSD relapse6–12 and evaluated pregnancy complications and outcomes.7–10 13–15 19 Several researchers tried to identify the risk factors for a pregnancy-related attack7 13 15 and another one investigated the effect of NMOSD on miscarriage and pre-eclampsia in AQP4-ab-positive patients.10 Compared with the aforementioned studies, ours entailed the largest cohort to explicitly summarise the pregnancy-related attack using univariate and multivariate logistic regression

### Table 4  Risk factors of pregnancy-related attack using univariate and multivariate logistic regression

| Variable | Univariate analysis | Multivariate analysis |
|----------|---------------------|-----------------------|
|          | OR (95% CI)         | P value               | OR (95% CI)         | P value               |
| Age at disease onset (76) | 0.90 (0.83–0.99) | 0.027** | — | 0.799 |
| Age at delivery/abortion | 1.00 | 1.00 | — | —  |
| 33–40 (12) | 36.67 (4.15–323.86) | 0.001** | 43.61 (4.26–446.91) | 0.001** |
| 26.5–33 (39) | 34.83 (37.0–328.33) | 0.002** | 17.32 (1.64–182.83) | 0.018* |
| 20–26.5 (25) | 1.04 (0.90–1.19) | 0.598 | — | —  |
| Time interval from pregnancy to disease onset (76) | 1.01 (0.99–1.03) | 0.289 | — | —  |
| Treatment during pregnancy and after delivery/abortion | — | — | — | —  |
| Adequate treatment† (10) | 1.00 | 1.00 | — | —  |
| Inadequate treatment‡ (66) | 10.67 (2.07–55.07) | 0.005** | 18.45 (2.60–131.19) | 0.004** |
| AQP4-ab titre | — | — | — | —  |
| <1:100 or negative (45) | 1.00 | 1.00 | — | —  |
| ≥1:100 (31) | 4.55 (1.48–13.97) | 0.008** | 4.20 (1.01–17.50) | 0.049* |
| Relapse within 1 year before pregnancy | — | — | — | —  |
| No (58) | 1.00 | — | — | —  |
| Yes (18) | 0.56 (0.19–1.66) | 0.298 | — | —  |
| ARR before pregnancy (76) | 0.57 (0.17–1.95) | 0.373 | — | —  |
| EDSS score before pregnancy (76) | 0.96 (0.68–1.34) | 0.808 | — | —  |
| Counts of concomitant auto-antibodies§ | — | — | — | —  |
| <1 (42) | 1.00 | — | — | —  |
| ≥1 (34) | 1.48 (0.56–3.88) | 0.429 | — | —  |
| Counts of concomitant auto-antibodies§ | — | — | — | —  |
| <2 (51) | 1.00 | — | — | —  |
| ≥2 (25) | 1.16 (0.42–3.21) | 0.776 | — | —  |

*P<0.05; **p<0.01.
†Adequate treatment was defined as (1) usage of relatively higher dose oral prednisone (>10 mg/day), and (2) usage of immunosuppressant (azathioprine 100 mg/day or tacrolimus 3 mg/day) combined with or without oral steroid, (3) a dose of rituximab (375 mg/m2) within 6 months before conception and shortly after delivery.
‡Inadequate treatment referred to (1) no treatment at all, (2) usage of low-dose oral prednisone (<10 mg/day) combined with or without oral steroid, (3) a dose of rituximab (375 mg/m2) within 6 months before conception and shortly after delivery.
§including antinuclear antibody, extractable nuclear antigen antibody, double-stranded DNA antibody, antineutrophil cytoplasmic antibody, antithyroid peroxidase antibody and thyroglobulin antibody.

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of the occurrence of pregnancy-related attacks. The results indicated that patients with younger age at delivery-abortion, higher AQP4-ab titre were at higher risk for pregnancy-related attack and maintenance therapy with appropriate immunosuppressant or sufficient dose of oral steroid should be performed during pregnancy and postpartum period. Previous studies also explored the risk factors for pregnancy-related attacks. Shimizu et al observed that an increased risk of pregnancy-related attack was associated with having a relapse during 1 year before pregnancy and discontinued or low-dose immunosuppressive therapy. Huang et al reported that negative AQP4-ab, concomitance with autoimmune diseases/antibodies, and no treatment in remission were risk factors for pregnancy-related recurrence. Recently, Kim et al showed that discontinuation of oral immunosuppressant in order to become pregnant appeared to increase the risk of pregnancy-related attack while pregnancy-related attack was negatively associated with pregnancy after initiation of rituximab. There are some discrepancies among the results of these studies, which may originate from the different features of the study cohorts including sample size, ethnicity or baseline disease activity. Similar to previous investigation, we did not observe significant correlation between the prepregnancy ARR and the risk of pregnancy-related attack.

Because of the retrospective nature, the timings of AQP4-ab detection vary among individuals, which constitutes a major limitation of our study. To minimise the possible impact of antibody titre fluctuation over time on the study results, we used the earliest available AQP4-ab titres detected in a remission status in the univariate and multivariate analyses of potential risk factors. This AQP4-ab titre, though not perfect, might reflect the primordial face of individual autoimmune conditions and was least affected by immunosuppressant treatments in a real-world setting. Our results indicated that physicians might need to pay enough attention to the risk of pregnancy-related attack in patients with higher AQP4-ab titre.

We further provided a nomogram to predict the probability of pregnancy-related attack. Previous studies showed that nomograms were superior to conventional staging systems for prognosis prediction of some cancers. In our nomogram generated from the primary cohort, the calibration curve demonstrated good agreement, while the C-index (0.87 and 0.77) exhibited good discrimination using bootstrap resampling in internal and external validation. This could provide an efficient reference when counselling patients with NMOSD about pregnancy issues.

We also demonstrated that compared with the AQP4 cohort, the pregnancy-related attack in MOG cohort exhibited more optic neuritis, less acute myelitis and lower EDSS scores in the remission phase. These features appear to be consistent with previous reports on the comparison of clinical manifestations and outcomes between the two disease entities. Limited by the relative rarity of MOG-ab positivity, we had insufficient number of patients with MOG-ab manifesting the onset of disease before pregnancy.

To conclude, our study showed that pregnancy-related NMOSD attacks were most common during 0–3 months after delivery-abortion and we identified independent risk factors for pregnancy-related attacks. The primary limitation of our study included its retrospective nature, small number of MOG subsets. Besides, AQP4-ab titres were not detected at fixed time points after NMOSD onset. Future prospective studies with larger sample size and protocol defined timing of antibody detection are therefore warranted to confirm and extend our findings.
Table 5  The comparison of pregnancy-related attack between patients with NMOSD with AQP4-ab and MOG-ab

|                          | AQP4 cohort | MOG cohort | P value |
|--------------------------|-------------|------------|---------|
| Number of patients       | 42          | 16         | —       |
| Age at disease onset, year, median (range) | 27.9 (20.6–42.8) | 28.3 (22.9–38.0) | 0.727  |
| Age at delivery-abortion, year, median (range) | 27.9 (20.1–42.7) | 28.3 (23.0–37.2) | 0.793  |
| Number of pregnancy-related attacks, median (range) | 1 (1–4) | 1 (1–3) | 0.944  |
| Number of pregnancy-related attacks, n (%) | | | |
| DP1                      | 4 (6.3)     | 2 (8.3)    | 0.666   |
| DP2                      | 2 (3.2)     | 0 (0)      | 1.000   |
| DP3                      | 2 (3.2)     | 0 (0)      | 1.000   |
| PP1                      | 25 (39.7)   | 9 (37.5)   | 0.852   |
| PP2                      | 15 (23.8)   | 4 (16.7)   | 0.471   |
| PP3+4                    | 15 (23.8)   | 9 (37.5)   | 0.202   |
| Type of pregnancy-related attacks, n (%) | | | |
| Optic neuritis            | 24 (38.1)   | 19 (39.2)  | <0.001** |
| Acute myelitis            | 33 (52.4)   | 6 (25.0)   | 0.022   |
| Area postrema syndrome    | 16 (25.4)   | 1 (4.2)    | 0.054   |
| Acute brainstem syndrome  | 3 (4.8)     | 0 (0)      | 0.558   |
| Patient with concomitant auto-antibodies, n (%) | 23 (54.8) | 2 (12.5) | 0.004** |
| ANA                      | 20 (47.6)   | 1 (6.3)    | 0.003** |
| EMA-ab                   | 13 (31.0)   | 1 (6.3)    | 0.105   |
| dsDNA-ab                 | 2 (4.8)     | 0 (0)      | 1.000   |
| ANCA                     | 0 (0)       | 0 (0)      | —       |
| ACA                      | 1 (2.4)     | 0 (0)      | 1.000   |
| TPO-ab and TG-ab         | 12 (28.6)   | 2 (12.5)   | 0.350   |
| EDSS score in exacerbation phase, median (range) | 4 (3–9) | 4 (3–7.5) | 0.428   |
| EDSS score in remission phase, median (range) | 2 (0–9) | 1 (0–7.5) | 0.003** |

*P< 0.05, **p< 0.01.
ACA, antiprophospholipid antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AQP4-ab, aquaporin-4 antibody; DP, during pregnancy; dsDNA-ab, double-stranded DNA antibody; EDSS, Expanded Disability Status Scale; EMA-ab, extractable nuclear antigen antibody; MOG-ab, myelin oligodendrocyte glycoprotein antibody; NMOSD, neuromyelitis optica spectrum disorder; PP, postpartum period; TG-ab, thyroglobulin antibody; TPO-ab, thyroid peroxidase antibody.

Contributors  LW designed and conceptualised the study, interpreted and analysed the data and drafted and reviewed the manuscript for intellectual content. LZ, JZ, WH and XC played a major role in the acquisition of data and revised the manuscript for intellectual content. CL and MW reviewed the manuscript for intellectual content. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests  LW, LZ, JZ, WH, XC, CL, MW, WL, JX, XL, LC, WQ, JL, CZ and CQ are sponsor of the current study and contributed to data interpretation. QL, JL and CZ revised the manuscript for intellectual content. CQ designed and conceptualised the study, interpreted and analysed the data and revised the manuscript for intellectual content. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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