Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods. Search Strategy for Neuromyelitis Optica

**Medline, PubMed in-process and non-Medline Strategy**

Exp pregnancy/ or exp fetus/ or exp pregnancy complications/ or exp infant, newborn/ or exp postpartum period/ or exp prenatal diagnosis/ or preconception care/ or (pregnan* or obstetric* or gestation*).tw. or (f?etus or f?etal).tw. or newborn.tw. or (new adj1 born).tw. or neonat*.tw. or infan*.tw. or birth*.tw. or childbirth*.tw. or (labo?t or puerper* or C?esar*).tw. or exp fetal development/ or exp fetal therapies or exp placental function tests/ or exp umbilical cord/ or exp prenatal diagnosis/ or exp fetal monitoring/ or exp perinatal care/ or exp obstetrical surgical procedures/ or exp anesthesia, obstetrical/ or exp analgesia, obstetrical/ or exp parity/ or exp apgar score/ or exp postpartum period/ or ((forcep* or vacuum or ventouse or instrument*) adj2 deliver*).tw. or (antepart* or ante-part* or prenat* or pre-nat* or perinat* or peri-nat* or peripart* or peri-part*).tw. or (postnat* or post-nat* or postpart* or post-part* or breastfe* or breast-fe* or (breast adj1 fe*)).tw. or obstetrics/

AND

Neuromyelitis Optica/ or Optic Neuritis/ or (devic or devic's or devics).mp. or neuromyelitis optica.mp. or neuromyletis optica.mp. or optic neuritis.mp. or (NMO or AQ4 or AQP4 or AQ 4 or AQP 4 or AQ-4 or AQP-4 ).mp. or Aquaporin 4/ or (aquaporin adj2 "4").mp.

**Embase Strategy**
Exp pregnancy/ or exp pregnancy disorder/ or exp pregnancy complication/ or exp pregnant women/ or exp newborn/ or (pregnan* or obstetric* or gestation*).tw. or (f?etus or f?etal).tw. or exp maternal care/ or exp puerperium/ or (newborn or (new adj1 born) or neonat* or infant*).tw. or (birth* or childbirth* or labo?r* or puerper* or c?esear* or episiotomy*).tw. or ((forcep* or vacuum or ventouse or instrument or vaginal) adj2 deliver*).tw. or (antepart* or ante-part* or prenat* or pre-nat* or antenat* or ante-nat* or perinat* or peri-nat or peripart* or peri-part*).tw. or (postnat* or post-nat* or postpart* or post-part* or lactat* or breastfe* or breast-fe*).tw. or (breast adj1 fe*).tw. or exp obstetric operation/ or exp anesthesia, obstetric/ or exp analgesia, obstetrical/ or exp parity/ or exp apgar score/ or exp postpartum period/or obstetrics/

AND

Myelooptic neuropathy/ or optic neuritis/ or (devic or devic's or devics).tw. or neuromyelitis optica.tw. or neuromyletis optica.tw. or optic neuritis.tw. or (transverse adj1 myelitis).tw. or (anti-aquaporin or anti-NMO or anti-neuromyelitis optica or anti-AQ4).tw. or aquaporin 4 antibody/

**Keyword Strategy for Web of Science and Cochrane**

(pregnan* or obstetric* or gestation*) or f?etus or f?etal or newborn or neonat* or infant* or birth* or childbirth* or labo?r* or puerper* or c?esear* or episiotomy* or forcep* or vacuum or ventouse or "instrument delivery" or "vaginal delivery" or
antepart* or ante-part* or prenat* or pre-nat* or antenat* or ante-nat* or perinat* or peri-nat or peripart* or peri-part* or postnat* or post-nat* or postpart* or post-part* or lactat* or breastfe* or breast-fe*

AND

Devic or devic's or devics or neuromyelitis optica or neuromyelitis optica or optic neuritis or transverse myelitis or anti-aquaporin or anti-NMO or anti-neuromyelitis optica or anti-AQ4
eAppendix. ARR at Each Phase, EDSS Score at Each Phase, and Pregnancy Outcomes and Complications

ARR at each phase

In subgroup analysis, we divided the patients with NMOSD into those with AQP4-Ab, MOG-Ab or seronegative status. There were six studies included into meta-analysis of patients with NMOSD with AQP4-Ab. The integrated ARR at each phase is exhibited in eFigure 4A in the Supplement. The highest ARR was 1.64 (95% CI, 1.23-2.05) in PP1, while the lowest ARR was 0.11 (95% CI, -0.01 to 0.23) in T1. It reached the statistical significance in ARR between before pregnancy and PP1 (MD, 1.19; 95% CI, 0.64-1.74; \( P < .001 \)), as well as before pregnancy and T1 (MD, -0.24; 95% CI, -0.42 to -0.07; \( P = .007 \)), before pregnancy and T2 (MD, -0.19; 95% CI, -0.33 to -0.05; \( P = .009 \)) (eFigure 5A, 5B, 5D in the Supplement). However, the differences in ARR were not significant between before pregnancy and the other phases of T3 (MD, -0.16; 95% CI, -0.36 to 0.05; \( P = .13 \)), PP2 (MD, 0.41; 95% CI, -0.01 to 0.83; \( P = 0.06 \)), PP3 (MD, -0.13; 95% CI, -0.31 to 0.05; \( P = .16 \)) (eFigure 5C, 5E, 5F in the Supplement).

In meta-analysis of patients with NMOSD with MOG-Ab, there were two studies included. The integrated ARR at each phase is presented in eFigure 4B in the Supplement. The highest ARR was 0.63 (95% CI, -0.04 to 1.30) in PP1, while the lowest ARR was 0 (95% CI, 0-0) in T1 and T3. It reached the statistical significance in ARR between before pregnancy and T1 or T3 (MD, -0.60; 95% CI, -1.06 to -0.15; \( P = .009 \)) (eFigure 6A, 6C in the Supplement). However, the differences in ARR were
not significant between before pregnancy and the other phases of T2 (MD, -0.28; 95% CI, -1.88 to 1.32; \(P = .73\)), PP1 (MD, -0.16; 95% CI, -0.79 to 0.48; \(P = .63\)), PP2 (MD, -0.23; 95% CI, -1.55 to 1.09; \(P = .73\)) and PP3 (MD, -0.31; 95% CI, -0.72 to 0.10; \(P = .13\)) (eFigure 6B, 6D, 6E, 6F in the Supplement).

There were two studies included into meta-analysis of patients with NMOSD with seronegative status.\(^7\) \(^,\) \(^27\) The integrated ARR at each phase is presented in eFigure 4C in the Supplement. The highest ARR was 0.83 (95% CI, -0.56 to 2.22) in PP1, while the lowest ARR was all 0 (95% CI, -0.01 to 0.01) in T1, T2 and T3. It reached the statistical significance in ARR between before pregnancy and T1, T2 or T3 (MD, -0.36; 95% CI, -0.62 to -0.10; \(P = .008\)) (eFigure 7A, 7B, 7C in the Supplement). However, the differences in ARR were not significant between before pregnancy and the other phases of PP1 (MD, 0.59; 95% CI, -1.03 to 2.21; \(P = .48\)), PP2 (MD, -0.03; 95% CI, -0.63 to 0.57; \(P = .92\)) and PP3 (MD, -0.22; 95% CI, -0.50 to 0.07; \(P = .13\)) (eFigure 7D, 7E, 7F in the Supplement).

**EDSS score at each phase**

In subgroup analysis, we divided the patients with NMOSD into the those with AQP4-Ab or without AQP4-Ab (including those with MOG-Ab and seronegative status). In meta-analysis of patients with NMOSD with AQP4-Ab, there were two studies included.\(^7\) \(^,\) \(^20\) The integrated EDSS score at each phase is presented in eFigure 4D in the Supplement. Compared to the EDSS score in before pregnancy, the increase in EDSS score of during pregnancy did not reach statistical significance (MD, 0.38; 95% CI, -0.08 to 0.84; \(P = .10\)) while that of postpartum was statistically significant.
(MD, 0.60; 95% CI, 0.20-1.01; \( P = .004 \)) (eFigure 8C, 8D in the Supplement).

There were two studies included into meta-analysis of patients with NMOSD without AQP4-Ab.\(^7^,\,20\) The integrated EDSS score at each phase is presented in eFigure 4E in the Supplement. Compared to the EDSS score in before pregnancy, the increase in EDSS scores of during pregnancy was not statistically significant (MD, 0.18; 95% CI, -0.33 to 0.70; \( P = .48 \)) while that of postpartum reached statistical significance (MD, 0.44; 95% CI, 0.03-0.86; \( P = .04 \)) (eFigure 8E, 8F in the Supplement).

**Pregnancy outcomes and complications**

Factors associated with spontaneous abortions, or neonatal complications are presented in eTable 2 in the Supplement. It was not statistically significant in the rate of pregnancies with spontaneous abortions (RR, 1.78; 95% CI, 0.80-3.96; \( P = .16 \)) or neonatal complications (RR, 1.98; 95% CI, 0.66-5.89; \( P = .22 \)) between the two groups receiving or without immunosuppressive treatment during pregnancy (eFigure 9A, 9B in the Supplement). In meta-regression analysis, the rate of pregnancies with spontaneous abortions did not reach statistical significance using the rate of immunosuppressive treatment during pregnancy (OR, 1.11; 95% CI, 0.85-1.45; \( P = .38 \)), age at conception (OR, 1.01; 95% CI, 0.98-1.04; \( P = .55 \)), or AQP4-Ab positivity rate (OR, 1.00; 95% CI, 1.00-1.00; \( P = .57 \)). The rate of pregnancies with neonatal complications did not reach statistical significance using the rate of immunosuppressive treatment during pregnancy (OR, 0.96; 95% CI, 0.76-1.21; \( P = .62 \)), age at conception (OR, 0.99; 95% CI, 0.97-1.00; \( P = .09 \)), or AQP4-Ab positivity rate (OR, 1.00; 95% CI,
1.00-1.00; \( P = .82 \).

**eFigure 1.** Forest Plot of Rates of Pregnancy With Pregnancy-Related Attacks in Patients With NMOSD

| Study ID | ES (95% CI) | Weight |
|----------|-------------|---------|
| Kim et al., 2012 | 0.81 (0.66, 0.96) | 9.31 |
| Shimizu et al., 2016 | 0.75 (0.51, 0.99) | 7.78 |
| Klauwer et al., 2017 | 0.59 (0.42, 0.75) | 9.10 |
| Shi et al., 2017 | 0.59 (0.39, 0.80) | 8.45 |
| Salvador et al., 2019 | 0.72 (0.58, 0.89) | 9.21 |
| Ashbani et al., 2020 | 0.75 (0.50, 0.94) | 8.71 |
| Kim et al., 2020 | 0.42 (0.26, 0.59) | 9.05 |
| Wang et al., 2020 | 0.66 (0.55, 0.76) | 9.92 |
| Collengues et al., 2021 | 0.40 (0.29, 0.52) | 9.79 |
| Dong et al., 2021 | 0.71 (0.55, 0.86) | 9.29 |
| Kemptel et al., 2021 | 0.08 (0.07, 0.22) | 9.41 |
| Overall (I-squared = 87.5%, \( p = 0.000 \)) | 0.59 (0.45, 0.72) | 100.00 |

**NOTE:** Weights are from random effects analysis.

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs.
The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Immunosuppressive treatment during pregnancy. B. Age at conception. C. AQP4-Ab. D. EDSS score at conception. E. Coexisting autoimmune disease. F. Relapse during the year before pregnancy. G. Age at disease onset. H. Time interval from disease onset to conception. NMOSD: neuromyelitis optica spectrum disorder; EDSS: Expanded Disability Status Scale; AQP4-Ab: anti-aquaporin-4 antibody.
**eFigure 3. Forest Plot of Differences in ARR of Patients With NMOSD Between Before Pregnancy and Other Phases**

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Difference in ARR between before pregnancy and T1. B. Difference in ARR between before pregnancy and T2. C. Difference in ARR between before pregnancy and T3. D. Difference in ARR between before pregnancy and T1. E. Difference in ARR between before pregnancy and PP3. ARR: annualized relapse rate; T1 indicates months 0 to 3 of pregnancy; T2, months 3 to 6 of pregnancy; T3, months 6 to 9 of pregnancy; PP1, months 0 to 3 of the postpartum period; PP2, months 3 to 6 of the postpartum period; PP3, months 6-12 of the postpartum period. Before pregnancy includes: 12 to 0 months before pregnancy.

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**eFigure 4.** Integrated ARR and EDSS Score in Patients With NMOSD With Different Antibody Status at Each Phase

Whiskers indicate 95% CIs. A. ARR in patients with NMOSD with AQP4-Ab. B. ARR in patients with NMOSD with MOG-Ab; C. ARR in patients with NMOSD with seronegative status; D. EDSS score in patients with NMOSD with AQP4-Ab. E. EDSS score in patients with NMOSD without AQP4-Ab. ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; T1 indicates months 0 to 3 of pregnancy; T2, months 3 to 6 of pregnancy; T3, months 6 to 9 of pregnancy; PP1, months 0 to 3 of the postpartum period; PP2, months 3 to 6 of the postpartum period; PP3, months 6 to 12 of the postpartum period. Before pregnancy includes: 12 to 0 months before pregnancy and postpartum, months 0 to 12 after pregnancy. *P < .05; **P < .01.
**eFigure 5.** Forest Plot of Differences in ARR of Patients With AQP4-Ab Between Before Pregnancy and Other Phases

**A.** Difference in ARR between before pregnancy and T1. **B.** Difference in ARR between before pregnancy and T2. **C.** Difference in ARR between before pregnancy and T3. **D.** Difference in ARR between before pregnancy and PP1. **E.** Difference in ARR between before pregnancy and PP2. **F.** Difference in ARR between before pregnancy and PP3. ARR, annualized relapse rate; T1 indicates months 0 to 3 of pregnancy; T2, months 3 to 6 of pregnancy; T3, months 6 to 9 of pregnancy; PP1, months 0 to 3 of the postpartum period; PP2, months 3 to 6 of the postpartum period; PP3, months 6 to 12 of the postpartum period. Before pregnancy includes: 12 to 0 months before pregnancy.

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs.
eFigure 6. Forest Plot of Differences in ARR of Patients With MOG-Ab Between Before Pregnancy and Other Phases

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Difference in ARR between before pregnancy and T1. B. Difference in ARR between before pregnancy and T2. C. Difference in ARR between before pregnancy and T3. D. Difference in ARR between before pregnancy and PP1. E. Difference in ARR between before pregnancy and PP2. F. Difference in ARR between before pregnancy and PP3. ARR: annualized relapse rate; T1 indicates months 0 to 3 of pregnancy; T2, months 3 to 6 of pregnancy; T3, months 6 to 9 of pregnancy; PP1, months 0 to 3 of the postpartum period; PP2, months 3 to 6 of the postpartum period; PP3, months 6-12 of the postpartum period. Before pregnancy includes: 12 to 0 months before pregnancy.

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eFigure 7. Forest Plot of Differences in ARR of Patients Who Were Seronegative Between Before Pregnancy and Other Phases

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Difference in ARR between before pregnancy and T1. B. Difference in ARR between before pregnancy and T2. C. Difference in ARR between before pregnancy and T3. D. Difference in ARR between before pregnancy and PP1. E. Difference in ARR between before pregnancy and PP2. F. Difference in ARR between before pregnancy and PP3. ARR: annualized relapse rate; T1 indicates months 0 to 3 of pregnancy; T2, months 3 to 6 of pregnancy; T3: months 6 to 9 of pregnancy; PP1: months 0 to 3 of the postpartum period; PP2: months 3 to 6 of the postpartum period; PP3, months 6 to 12 of the postpartum period. Before pregnancy includes: 12 to 0 months before pregnancy.
The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Difference in EDSS score between before pregnancy and during pregnancy in all patients with NMOSD. B. Difference in EDSS score between before pregnancy and postpartum in all patients with NMOSD. C. Difference in EDSS score between before pregnancy and during pregnancy in patients with NMOSD with AQP4-Ab. D. Difference in EDSS score between before pregnancy and during pregnancy in patients with NMOSD with AQP4-Ab. E. Difference in EDSS score between before pregnancy and during pregnancy in patients with NMOSD without AQP4-Ab. F. Difference in EDSS score between before pregnancy and postpartum in patients with NMOSD without AQP4-Ab. EDSS: Expanded Disability Status Scale; Before
pregnancy includes: 12 to 0 months before pregnancy and postpartum, months 0 to 12 after pregnancy.
**eFigure 9. Forest Plot of Immunosuppressive Treatment During Pregnancy on Spontaneous Abortions, or Neonatal Complications in Patients With NMOSD**

### A

| Study | RR (%) | Confidence Interval | Weight |
|-------|--------|---------------------|--------|
| Wu et al. 2017 | 3.97 (1.19, 12.91) | 7.45 |
| Schubert et al. 2019 | 2.84 (0.22, 35.32) | 12.50 |
| Kuo et al. 2018 | 1.34 (0.76, 2.34) | 26.63 |
| Wang et al. 2020 | 2.00 (0.14, 22.09) | 8.46 |
| Cataluppo et al. 2011 | 5.73 (0.85, 3.52) | 57.75 |
| Ding et al. 2021 | 0.64 (0.12, 3.58) | 6.11 |
| Overall (p-rep = 1.00, p = 0.01) | 1.70 (0.38, 7.85) | 100.00 |

**NOTE:** Weights are from random-effects analysis.

### B

| Study | RR (%) | Confidence Interval | Weight |
|-------|--------|---------------------|--------|
| Wang et al. 2016 | 3.80 (1.03, 13.20) | 13.22 |
| Wu et al. 2017 | 2.84 (0.22, 35.32) | 12.50 |
| Schubert et al. 2019 | 1.34 (0.76, 2.34) | 26.63 |
| Kuo et al. 2018 | 2.53 (1.56, 4.07) | 27.76 |
| Wang et al. 2020 | 0.64 (0.12, 3.58) | 6.11 |
| Ding et al. 2021 | 0.64 (0.12, 3.58) | 6.11 |
| Overall (p-rep = 1.00, p = 0.01) | 1.70 (0.38, 7.85) | 100.00 |

**NOTE:** Weights are from random-effects analysis.

The shaded boxes around the effect sizes represent the weight of each study and whiskers indicate 95% CIs. A. Spontaneous abortions. B. Neonatal complications.
**eFigure 10.** Funnel Plot of Publication Bias

The distribution of the points indicates publication bias of the included studies.
### eTable 1. Interaction Between Associated Factors on Pregnancy-Related Neuromyelitis Optica Spectrum Disorder Attacks

| Associated Factors                                           | No. of studies | No. of pregnancies | No. of events | P value |
|--------------------------------------------------------------|----------------|--------------------|---------------|---------|
| Rate of immunosuppressive treatment during pregnancy & Age at conception | 6              | 244                | 137           | .81     |
| Rate of immunosuppressive treatment during pregnancy & Age at disease onset | 6              | 244                | 137           | .55     |
| Rate of immunosuppressive treatment during pregnancy & ARR before pregnancy | 6              | 241                | 145           | .36     |
| ARR before pregnancy & Age at conception                    | 6              | 237                | 144           | .13     |
| ARR before pregnancy & Age at disease onset                 | 7              | 271                | 164           | .99     |
| Age at conception & Age at disease onset                    | 7              | 270                | 158           | .48     |

Abbreviations: ARR, annualized relapse rate.

### eTable 2. Factors Associated With Spontaneous Abortions, or Neonatal Complications

| Associated factors                                           | No. of studies | No. of pregnancies | No. of events | Effect size | 95% CI     | P value |
|--------------------------------------------------------------|----------------|--------------------|---------------|-------------|------------|---------|
| Immunosuppressive treatment during pregnancy †               | 7              | 274                | 23            | RR: 1.78    | 0.80-3.96  | .16     |
| Immunosuppressive treatment during pregnancy ‡               | 6              | 207                | 13            | RR: 1.98    | 0.66-5.89  | .22     |
| Rate of immunosuppressive treatment during pregnancy †       | 8              | 287                | 24            | OR: 1.11    | 0.85-1.45  | .38     |
| Rate of immunosuppressive treatment during pregnancy ‡       | 6              | 207                | 13            | OR: 0.96    | 0.76-1.21  | .62     |
| Age at conception †                                         | 9              | 364                | 29            | OR: 1.01    | 0.98-1.04  | .55     |
| Age at conception ‡                                         | 8              | 307                | 23            | OR: 0.99    | 0.97-1.00  | .09     |
| AQP4-Ab positivity rate †                                    | 11             | 443                | 45            | OR: 1.00    | 1.00-1.00  | .57     |
| AQP4-Ab positivity rate ‡                                    | 11             | 403                | 31            | OR: 1.00    | 1.00-1.00  | .82     |

Abbreviations: AQP4-Ab, anti-aquaporin-4 antibody; RR, risk ratio; OR, odds ratio; †Rate of pregnancies with spontaneous abortions; ‡Rate of pregnancies with neonatal complications.
eTable 3. The Newcastle-Ottawa Scale for Quality Appraisal of the Included Studies

| Study                  | Selection | Comparability | Outcome | Total score |
|------------------------|-----------|---------------|---------|-------------|
|                        | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Long enough follow-up for outcomes to occur | Adequacy of follow-up of cohorts |
| Bourre et al,8 2012    | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 8            |
| Kim et al,4 2012       | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Fragoso et al,9 2013   | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 7            |
| Nour et al,5 2016      | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 8            |
| Shimizu et al,4 2016   | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Huang et al,21 2017    | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Klawiter et al,22 2017 | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 6            |
| Shi et al,20 2017      | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 8            |
| Salvador et al,21 2019 | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Ashtari et al,23 2020  | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 7            |
| Kim et al,24 2020      | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Wang et al,2 2020      | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Collongues et al,27 2021 | ☆   | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Deng et al,2 2021      | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 9            |
| Kümpfel et al,28 2021  | ☆         | ☆             | ☆       | ☆          | ☆                       | ☆                     | ☆          | ☆                     | 7            |

The total score ranges from 0 to 9 stars. A score of 6 or higher corresponds to low risk of bias.