EPMA Journal (2018) 9:249–256
https://doi.org/10.1007/s13167-018-0143-9

REVIEW

Neuromyelitis optica spectrum disorders and pregnancy: relapse-preventive measures and personalized treatment strategies

Nadja Borisow[1] · Kerstin Hellwig[2] · Friedemann Paul[1,3]

Received: 24 May 2018 / Accepted: 11 July 2018 / Published online: 10 August 2018

Abstract

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune inflammatory diseases of the central nervous system that predominately affect women. Some of these patients are of childbearing age at NMOSD onset. This study reviews, on the one hand, the role NMOSD play in fertility, pregnancy complications and pregnancy outcome, and on the other, the effect of pregnancy on NMOSD disease course and treatment options available during pregnancy. Animal studies show lower fertility rates in NMOSD; however, investigations into fertility in NMOSD patients are lacking. Pregnancies in NMOSD patients are associated with increased disease activity and more severe disability postpartum. Some studies found higher risks of pregnancy complications, e.g., miscarriages and preeclampsia. Acute relapses during pregnancy can be treated with methylprednisolone and/or plasma exchange/immunoadsorption. A decision to either stop or continue immunosuppressive therapy with azathioprine or rituximab during pregnancy should be evaluated carefully and factor in the patient's history of disease activity. To this end, involving neuroimmunological specialist centers in the treatment and care of pregnant NMOSD patients is recommended, particularly in specific situations like pregnancy.

Keywords Neuromyelitis optica · Devic's syndrome · Pregnancy · Relapse prevention · Personalized treatment

Introduction

Neuromyelitis-optica-spectrum disorder (NMOSD) is an inflammatory CNS disease mediated by antibodies against the CNS water channel aquaporin-4 (AQP4). It is characterized by severe optic neuritis, myelitis, and less frequently, brainstem encephalitis [1–4]. NMOSD is more prevalent in women than men at a ratio of 3–9:1 [5–9]. A proportion of female patients experience NMOSD onset in their childbearing years (15 to 40 years), and in such cases, the treating neurologist is forced to address how the disease and its treatment may affect family planning and pregnancy.

Prior to the discovery in 2004 of the antibody to the astrocytic water channel AQP4, NMOSD had been categorized as a variant of multiple sclerosis (MS). Since then, numerous immunological imaging and animal studies have demonstrated that NMOSD is pathogenetically distinct from MS [6, 10–26]. In some cases, AQP4 antibodies cannot be detected, despite the patient presenting with clinical symptoms of NMOSD. Whether AQP4 antibody-positive and AQP4 antibody-negative diseases are variants of the same disorder or are distinct disease entities remains controversial.

Thanks to observational studies and pregnancy registries, data on how pregnancy affects MS disease course has accumulated over recent years. It is now known that the MS relapse rate is significantly reduced during pregnancy, particularly in the third trimester [27, 28]. In the first few months following delivery, the relapse rate then increases to a level higher than that prior to pregnancy [28]. The immunological processes underlying this phenomenon are the object of current research.

✉ Nadja Borisow
nadja.borisow@charite.de

[1] NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charitéplatz 1, 10117 Berlin, Germany

[2] Clinic for Neurology, St. Josef Hospital, Ruhr Universität Bochum, Bochum, Germany

[3] Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany

In contrast, far fewer data exist on pregnancy during NMOSD. Academic collaborations, like the German Neuromyelitis optica study group (NEMOS, www.nemos-net.de), are essential to collect data on NMOSD disease course including therapeutically challenging situations like pregnancies. In a South Korean study, 13 of 40 pregnancies (33%) were electively aborted, which can presumably be attributed to lack of experience and evidence-based guidelines on the possible effect of NMOSD on pregnancy outcome [29]. Therefore, a change from delayed interventional to preventive and individualized medicine is required. The concept of predictive, preventive, and personalized medicine (PPPM) is of particular importance in serious diseases such as NMOSD and receives additional relevance for patients planning families.

We here provide an overview of fertility, pregnancy course, and NMOSD treatment options during pregnancy. This article represents an English update of a German review recently published in *Der Nervenarzt* [30].

In recent years, several papers have demonstrated serum antibodies against myelin oligodendrocyte glycoprotein (MOG) in not only some AQP4 antibody-seronegative NMOSD patients but also individual MS patients [31–39]. Detailed characterization of the clinical phenotype, disease course, and treatment response of patients with MOG antibodies as well as a nosologic definition are currently the subject of intensive research and, in some cases, also controversial debate [40–46]. As no specific data on pregnancy in MOG antibody-positive patients currently exists, the present paper does not focus on this further.

Influence of NMOSD on fertility

AQP4 is a membrane protein and is expressed in the CNS and the optic nerve, in the spinal cord, as well as in the hypothalamus [47]. The hypothalamus is responsible for the formation of the gonadotropin-releasing hormone (GnRH), which influences the secretion of the sexual hormones. Consequently, AQP4 antibodies could also affect hormone levels and the fertility of NMOSD patients.

In studies of AQP4-knockout mice, significantly lower estrogen and progestogen serum levels were detected than in wild-type mice [48]. AQP4 deficiency damaged both oocyte development and endometrial thickness and led to subfertility and fewer offspring [49].

Few studies have been conducted on the fertility of NMOSD patients to date. In a study by Bove et al. of previous pregnancies in 217 NMOSD patients [6], 12 (6%) reported undergoing fertility treatment and 13% reported delayed achievement of pregnancy of > 12 months. However, the average age of the 217 patients at NMOSD onset was 40 years and the average age when first attempting to conceive was not reported. Therefore, a bias is possible as the higher average age of the study participants may be the reason for the subfertility. Moreover, only a few of the reported pregnancies occurred after the onset of NMOSD, and a large proportion of the patients had already completed their families at NMOSD onset. As such, further studies are needed to investigate the frequency of possible sub- and infertility in NMOSD patients.

Influence of pregnancy on disease course

NMOSD relapses are frequently accompanied by serious neurological deficits and the symptoms often only recede partially, leading to a rapid accumulation of neurological disability [50, 51]. From the perspective of preventive medicine, it is of particular relevance for patients planning families, whether and to what extent pregnancy poses a risk.

A recent retrospective study of 46 pregnancies in 31 NMO patients indicated increased disease activity, both during the first trimester and during the first 3 months after delivery [52]. Further studies have also shown an increased rate of relapse in the first 3 months [53–55] and 6 months [29] after delivery. Here, particularly patients without or with only low-dose immunosuppressive treatment experienced new relapses [29, 55].

To evaluate the long-term consequences of a pregnancy, the degree of disability is assessed using Expanded Disability Status Scale (EDSS), as is the case in MS. Bourre et al. found that EDSS scores increased from an average of 1.5 (± 1.7) prior to delivery to 2.6 (± 1.9) 1 year after childbirth [56]. A Brazilian study found an increase from 1.33 (± 1.6) prior to achieving pregnancy to 3.01 (± 1.83) after delivery [53].

NMOSD disease activity does not appear to be affected by the method of delivery, epidural administration, or breastfeeding [29, 56]. Table 1 summarizes the results of the case series of pregnant NMOSD patients published to date. It should be noted that some studies only include AQP4 antibody-positive patients [29, 54, 55], while others also include AQP4 antibody-negative patients [52, 56].

The causes of the negative effects of a pregnancy on NMOSD have not yet been sufficiently investigated. High estrogen levels during pregnancy stimulate immunoglobulin production and influence the glycosylation of antibodies and the formation of antibody-producing B cells [57]. Th2-mediated immune response increases during pregnancy, which, while facilitating maintenance of pregnancy, is also a known factor in NMOSD pathogenesis [57]. To date, no data exist on the influence of AQP4-antibody serostatus on pregnancy course.

Overall, the currently available literature indicates that pregnancy negatively influences NMOSD disease course, above all due to the increased relapse rate towards the end of a pregnancy and in early postpartum months. Patients desiring to have children should be comprehensively informed of this to weigh the potential risks.

Table 1 Published clinical series of pregnant NMOSD patients

Author	Year	Number of pregnancies	Number of patients	AQP4 antibody-positive patients	Results
Bourre et al. [56]	2012	25	20	8/19 (53%)[a]	Higher EDSS after pregnancy, no significant change in relapse rate during or following pregnancy
Kim et al. [29]	2012	54	40	40/40 (100%)	Increased relapse rate in the first 6 months after delivery; high relapse risk in patients not undergoing treatment; high rate of elective abortions; one premature birth in the third trimester with malformations
Fragoso et al. [53]	2013	17	17	n.a.	Higher EDSS after pregnancy; increased relapse rate in the first 3 months after delivery; no indications of malformation; diminished birth weight and length
Shimizu et al. [55]	2015	56	47	47/47 (100%)	Increased relapse rate in the first 3 months after delivery; AQP4 antibodies found in newborns, no longer detectable after 1 or 3 months, as applies
Nour et al. [54]	2016	126	60	60/60 (100%)	Increased relapse rate in the first 3 months after delivery; high rate of miscarriages (43%) for pregnancies after NMOSD onset, one child with hydrocephalus and permanent neurological disability
Klawiter et al. [52]	2017	46	31	25/31 (81%)	Increased relapse rate in the first trimester and in the first 3 months after delivery

EDSS Expanded Disability Status Scale, *AQP4-Ak* aquaporin4 antibodies, *NMOSD* neuromyelitis optica spectrum disorder, *n.a.* not applicable

[a] AQP4-antibody serostatus only available for 19/20 patients

Pregnancy course and outcome in NMOSD patients

In pregnant NMOSD patients, multidisciplinary approaches are required to ensure an optimized and personalized medical care. Patients should be advised that pregnancy complications, such as miscarriages and preeclampsia are possible. Early case reports between 1999 and 2014 found no indications of such complications in NMOSD patients [58–60]; however, a 2015 retrospective case series by Nour et al. found an increased rate of miscarriage [54]. In 6 of 14 pregnancies (43%) after NMOSD onset, miscarriage occurred within the first 24 weeks of pregnancy. In comparison, prior to disease onset, the rate of miscarriage was only 7%. Of the patients who miscarried, disease activity was significantly higher from 9 months prior to achieving pregnancy until the end of pregnancy than in patients with full-term pregnancies. A cause of the miscarriages could have been damaged to the placenta by circulating AQP4 antibodies. AQP4 is expressed in the placenta by syncytiotrophoblasts, particularly during the second trimester. Animal studies have shown that AQP4 antibodies are able to pass the blood-placenta barrier and bind to placenta AQP4, leading to inflammatory changes, placental necrosis, and an increased rate of miscarriage [61].

Reuss et al. describe the case of a 23-year-old NMOSD patient, who miscarried in the 21st week of pregnancy [62]. The fetus itself showed no abnormalities; however, analysis of the placenta demonstrated multiple infarcts, while AQP4-immunostaining showed complete loss of immunoreactivity. A recent Chinese study showed AQP4 immunoreactivity and signs of inflammation and damage in placentae of pregnancies electively terminated during the first and second trimester [63]. In contrast to that, term placentae revealed none of these abnormalities [63].

Data on the frequency of preeclampsia in NMOSD patients is lacking. In a study of 60 NMOSD patients, preeclampsia occurred in 11.5% of 126 pregnancies [54] which is significantly higher than the rate of 3% in the general population. No differences were found between pregnancies before and after NMOSD onset. No data exist to date on other possible pregnancy complications, such as hyperemesis gravidarum and gestational diabetes.

A Brazilian study provided data on the newborn physical examinations of eight children of NMOSD patients [53]. The average birth weight was 3425 g (2850–3910 g), while the average height at birth was 49.5 cm (48–51 cm). All eight children scored 9 to 10 points on the APGAR scale after 5 min and exhibited no abnormalities.

The study by Nour et al., on the other hand, reported one infant with severe hydrocephalus and permanent neurologic disability [54]. A further study reported a premature birth in the third trimester with birth defects, which were, however, not described in detail [29]. Other studies, which together included approximately 100 pregnancies, did not report any abnormalities [53, 55, 56].

As AQP4 antibodies can pass through the blood-placenta barrier, they can also be identified in the blood of the newborns of NMOSD patients after birth [55, 64]. However, an

increased AQP4 antibody titer in these children is generally not accompanied by neurological symptoms and normalizes within 3 to 6 months after birth [55, 64].

NMOSD in the mother might be accompanied by further autoimmune diseases [65, 66]. Acetylcholine receptor Abs or Anti-Ro Abs can be transmitted via the placenta and cause neonatal myasthenia gravis, systemic lupus erythematodes (SLE), or Sjögren's syndrome. Neonatal SLE and Sjögren's syndrome can lead to congenital heart block and in some children implantation of pacemaker may be necessary [67, 68]. Therefore, it is reasonable to search for Anti-Ro Abs during pregnancy and, in case of a positive result, to perform close sonographic fetal monitoring.

Treatment options during pregnancy

Due to the rarity of NMOSD, no treatment guidelines based on controlled clinical studies exist for NMOSD patients, including pregnant women. However, especially during pregnancy, a personalized treatment regimen is required. Hence, the recommendations found in current literature largely rely on retrospective data, case reports, and prospective observational studies.

One established treatment of acute NMOSD relapses outside of pregnancy is intravenous administration of 1 g methylprednisolone/day over five consecutive days [69, 70]. In cases of poor response to this therapy, 5 to 7 cycles of plasma exchange [70–73] or, alternatively, immunoadsorption [69, 73, 74] is recommended. Plasma exchange involves separating blood plasma from other blood components and simultaneously replacing it with a human albumin solution or fresh plasma. Possible complications include allergic reactions, low blood pressure, infections, hemorrhaging, and coagulation disorders. During immunoadsorption, the plasma is run through special apheresis columns, to which antibodies and immune complexes are bound. Subsequently, the plasma, now purified of the antibodies, is reinfused. Possible risks include allergic reactions and blood pressure dysregulation.

Given careful risk-benefit analysis, methylprednisolone, plasma exchange, and immunoadsorption can also be administered during pregnancy [75, 76]. Possible risks of glucocorticoid treatment include gestational diabetes, thrombosis, and psychiatric disturbances; a slightly increased risk of orofacial cleft in newborns has been described for administration in the first trimester [76, 77]. However, the latter refers to long-term methylprednisolone therapy, in which a maintenance treatment of 8–12 mg per day should not be exceeded [77]. In contrast, no dosage constraints exist for emergency treatment and when treating acute symptoms [77]. However, no data exist on short-term treatment with methylprednisolone during pregnancy.

Reports on treatment by plasma exchange during pregnancy are available for patients with antiphospholipid antibody syndrome [78, 79] and thrombotic thrombocytopenic purpura [80, 81]. As long as any pregnancy-related requirements (e.g., lying on the left side, adjustment of the plasma volume [82]) are taken into account, plasma exchange is a low-complication alternative treatment or escalation therapy in cases of severe or treatment-resistant NMOSD relapse during pregnancy.

Immunoadsorption has also been applied for various autoimmune diseases during pregnancy, including MS [75] and SLE [83]. The advantages of this treatment compared to plasma exchange include less risk of infection and allergic reaction. However, to date, far fewer data exist on the therapeutic benefit of immunoadsorption compared to plasma exchange in NMOSD [74].

For non-pregnant NMOSD patients, currently favored long-term treatment includes azathioprine (AZA) and rituximab (RTX) [69, 84–87]. Much data has accumulated on the use of AZA during pregnancy, particularly from clinical series and observational studies of chronic inflammatory bowel diseases or postorgan transplantation care [77, 88–90]. While the data does not point to any teratogenic risk, some indications for a higher rate of premature births and lower birth weight [77, 89, 91] exist. However, the latter could also be caused by the individual underlying disease or other drugs administered as part of the treatment plan. Case reports describe bone marrow suppression with anemia and severe lympho- and pancytopenia in infants after maternal AZA exposure [92–94]. Because rare side effects cannot be ruled out, the risk of relapse by stopping or reducing AZA treatment should be carefully weighed against the possible risk to the child by continuing the treatment. Critical factors to consider as part of this are the relapse rate before pregnancy, the severity of the relapses, and the relapse remission to realize an individually tailored treatment approach.

The little information that exists on RTX treatment during pregnancy is primarily found in case reports of rheumatological and hematological patients, as well as the manufacturer's drug safety database. According to the manufacturer, the average half-life of RTX is 20 to 32 days. As a monoclonal antibody, RTX can pass the blood-placenta barrier with increasing ease as pregnancy progresses and is detectable in umbilical cord blood of exposed newborns [95, 96]. Evidence suggests that RTX treatment carries a higher risk of premature births, although presumably, the underlying maternal illness should be considered the cause [77]. Even if no risk of abnormal fetal development is known, monitoring the pregnancy with regular, frequent ultrasound examinations is recommended to warrant early detection and prevention of

possible complications [77]. As RTX treatment during pregnancy also transiently depletes B cells in newborns [95, 96], measuring B lymphocyte levels of fetuses is advised if exposed to RTX after the first 20 weeks of pregnancy [77].

A case report by Pellkofer et al. describes an NMOSD patient who achieved pregnancy 1 week after the second RTX infusion had been administered [97]. With depletion of CD19+ B cells, the patient did not experience any relapses during the entire pregnancy; however, new attacks occurred 10 days postpartum and 2 months later. In a case report by Ringelstein et al., RTX administered 7 months prior to conception and 2 days after delivery prevented a relapse occurring during both pregnancy and postpartum [64]. A systematic review including more than 100 pregnancies with RTX use within 6 months of conception in MS and NMOSD did not show elevated rates of spontaneous abortion, malformations, or other major adverse effects [98].

Overall, careful risk-benefit analysis of stopping or continuing immunosuppressive treatment is necessary in patients planning families. Under the aspect of possibly preventive effects, patients with desire for children should try to conceive soon after RTX-administration to ensure a sustained RTX effect during pregnancy. If treatment with RTX is necessary after the 20th week of pregnancy, B cell depletion is likely to occur in the child. The real risk of infections under this therapy is not clear. Additionally, as described in the case report by Ringelstein et al. [64], resuming RTX treatment shortly after delivery can be considered as a measure of prevention, as pregnancy-associated relapses are more frequent and more severe in untreated patients [29, 55, 59].

Although only few case reports exist on relapse prevention using intravenous immunoglobulins (IVIG) [99–101], they can be considered an alternative to AZA and RTX if immunosuppressive treatment is contraindicated [69]. IVIG treatment is considered to be safe during pregnancy and breastfeeding and finds off-label use in the treatment of, for example, pregnant and breastfeeding MS patients [102].

Tocilizumab, a monoclonal antibody against the interleukin-6 receptor, is a another, new alternative when other treatments are not effective [103, 104]. Data on pregnancies using this medication are available for patients with rheumatological diseases from drug safety databases of clinical studies [105, 106]. An increased rate of premature births without clear indications for an increased risk of congenital abnormalities was reported.

Immunosuppressants, like methotrexate, mycophenolate mofetil, and mitoxantrone, which are used as second-line treatments in NMOSD, are strictly contraindicated during pregnancy due to their teratogenic potential and the high risk of miscarriage [77]. Treatment with mycophenolate mofetil should stop 6 weeks; methotrexate, 12 weeks; and mitoxantrone, 6 months before attempting to conceive.

Conclusion and expert recommendations

- Pregnancy carries the risk of relapse and subsequent disability for women with NMOSD, including possible triggering of relapses by the pregnancy, increased relapse frequency postpartum, and higher degree of disability after pregnancy.
- An NMOSD diagnosis confers increased risk of pregnancy complications, such as miscarriages and preeclampsia.
- Treatment of relapses is possible even during pregnancy using methylprednisolone and/or plasma exchange/immunoadsorption
- Careful and individualized risk-benefit analysis of stopping/continuing immunosuppressive treatment with AZA or RTX is mandatory, factoring in the patient's history of disease activity.
- Involvement of neuroimmunological specialist centers to ensure personalized treatment and care for NMOSD patients is strongly recommended, particularly to provide family planning counseling and advice on questions relating to pregnancy.
- In case of significant disease activity prior to conception with frequent and disabling relapses, most experts would probably advocate immunotherapy during pregnancy and after delivery, notwithstanding an individualized and tailored treatment decision in alignment with the patient's preferences.

Compliance with ethical standards

Ethical approval For this type of study, formal consent is not required.

Conflict of interest N. Borisow declares no conflict of interest.

F. Paul is a member of the scientific advisory board of Novartis; has received lecture fees and travel reimbursement from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is academic editor of PLoS One, Associate Editor of Neurology® Neuroimmunology & Neuroinflammation; consulted for Sanofi-Genzyme, Biogen Idec, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, the German Research Foundation, the Werth Foundation of the city of Cologne, the German Federal Ministry of Research and Education, the Arthur Arnstein Stiftung Berlin, the EU FP7 Framework Program, Jackson Charitable Foundation, and the National Multiple Sclerosis of the USA.

K. Hellwig received consultant and lecture fees and research support from Bayer Healthcare, Biogen, Novartis Pharma, Teva Pharma, Roche, and Sanofi-Genzyme und Merck.

The NEMOS cohort/NationNMO is supported by the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS; for NEMOS NationNMO-LAB FKZ 01GI1602A to B.W., NationNMO-PAT FKZ 01GI1602B to O.A., and NationNMO-DAB FKZ 01GI1602C to J.S.).

Human and animal studies This paper included no studies of humans or animals.

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