Gender issues of antibody-mediated diseases in neurology: (NMOSD/autoimmune encephalitis/MG)

Ayse Altintas, Justina Dargvainiene, Christiane Schneider-Gold, Nasrin Asgari, Ilya Ayzenberg, Andrea I. Ciplea, Ralf Junker, Frank Leypoldt, Klaus-Peter Wandinger and Kerstin Hellwig

Abstract: Neuromyelitis optica spectrum disorder (NMOSD), autoimmune encephalitis (AE), myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) are antibody-mediated neurological diseases. They have mostly female predominance, affecting many women during childbearing age. Interactions between the underlying disease (or necessary treatment) and pregnancy can occur in every of these illnesses. Herein, we present the characteristics of NMOSD, AE, MG and LEMS in general, and review published data regarding the influence of the different diseases on fertility, pregnancy, puerperium, treatment strategy during pregnancy and post-partum period, and menopause but also male factors. We summarise key elements that should be borne in mind when confronted with such cases.

Keywords: autoimmune encephalitis, Lambert-Eaton myasthenic syndrome, myasthenia gravis, neuromyelitis optica spectrum disease, pregnancy, sex differences, women

Introduction
Antibody-mediated neurological diseases are often seen dominantly in women. In others, male predominance can be observed, for example, autoimmune encephalitis (AE) with CASPR2-antibodies.

In this review, we consider gender issues regarding fertility, pregnancy, puerperium, treatment strategy during pregnancy and post-partum period and menopause in patients with neuromyelitis optica spectrum disorder (NMOSD), AE, myasthenia gravis (MG) or Lambert-Eaton myasthenic syndrome (LEMS).

Neuromyelitis optica spectrum disorder

General introduction
NMOSD is a rare autoantibody-associated disorder of the central nervous system (CNS). Antibodies play a decisive role in NMOSD pathogenesis, targeting the astrocytic water channel protein aquaporin-4 (AQP4-abs), classifying it as a primary autoimmune astrocytopathy with secondary demyelination and neuroaxonal damage.\(^1,2\) AQP4-abs can be found in the serum of approximately 80% of NMOSD patients, and only rarely in cerebrospinal fluid (CSF).\(^3\) Using a cell-based diagnostic assay is critical for correct diagnosis.\(^4\) Pathophysiological mechanisms underlying the seronegative variant remain mostly unclear, and probably differ from those in seropositive NMOSD. Approximately 20% of these patients have antibodies targeting full-length myelin oligodendrocyte glycoprotein (MOG), presenting an NMOSD-like phenotype of a distinct clinical entity: MOG-abs associated disease (MOGAD).\(^5-8\) There is a bidirectional association between seropositive NMOSD and several other autoimmune diseases, including systemic lupus erythematosus, primary Sjögren’s syndrome and MG. Recurring, and often severe, attacks of uni- or bilateral optic neuritis and myelitis are most typical clinical manifestations of
NMOSD. Other characteristic manifestations include, especially, area postrema syndrome, presenting as a triad of hiccup, nausea and vomiting, diencephalic syndrome (e.g. narcolepsy) or multiple sclerosis (MS)-atypical large or even tumefactive (>3 cm) cerebral lesions.9 Further typical brain lesions occur in the dorsal medulla and at periependymal surfaces (e.g. along aqueduct and third ventricle).10 CSF-restricted oligoclonal bands (OCBs) have been observed transiently in up to 30% of NMOSD patients, and less frequently compared with >95% in MS, where OCBs were shown to remain detectable over decades.11

In contrast to MS, the progressive course of AQP4- abs positive NMOSD is uncommon and disability is mostly attack-related. Acute attacks can be treated with a high-dose steroid pulse, apheresis therapies or both.12 Due to often incomplete recovery, especially in severe attacks, apheresis should be started as soon as possible as a first-line therapy.13,14 Long-term immunotherapy should be started early after disease manifestation. In the last decade, rituximab, azathioprine or mycophenolate mofetil have been used widely as first-line off-label therapies, whereby rituximab seems to be the most effective.15 Several recent phase III studies demonstrated high efficacy of three other monoclonal antibodies targeting complement factor C5 (eculizumab), IL6-receptor (satralizumab) or CD19 positive lymphocytes (inebilizumab), opening a new era in NMOSD treatment.16–20

Epidemiology focusing on gender aspects
Epidemiological studies in a disease as rare as NMOSD are challenging. Data on incidence and prevalence of NMOSD vary between different populations and geographic regions as well as depending on methodological aspects, diagnostic criteria sensitivity and availability of AQP4- abs testing.9,21,22 The overall prevalence of NMOSD lies between 0.3 and 4.4 per 100,000 (higher in Asian, South-American and African populations), with a clear female predominance.2 In seropositive patients, the female-to-male ratio is as high as 9:1–10:1.23 Despite occurring rarely in childhood and senescence, the median age of NMOSD onset is 39 years. Accordingly, around half of all patients are of child-bearing age. Hormonal changes occurring over a women’s lifespan significantly influence the risk of NMOSD. Borisow et al. investigated the differences in the female-to-male ratio between age groups in NMOSD, and differences in attack symptoms and treatment response in females with NMOSD during and after the reproductive period.24 In the AQP4- abs-positive group, female-to-male ratios were 3:1, 23:1, and 5:1 for age groups <15, 15–40, and >40 years, respectively. In contrast, in AQP4- abs-negative patients (n = 27, 15%), the female-to-male ratios were reported as 1:1.2 for age groups 15–40 and >40 years. No differences in clinical presentation could be detected between females and males. Complete remission after relapse and a better response to treatment were reported more frequently in younger (<40 years old) women. Bove et al. reported reproductive history and hormone use in a large population of women with NMOSD (n = 217).25 In contrast to MS, they could not demonstrate any clear relationship between endogenous hormonal exposures and age at NMOSD onset. However, an earlier disease onset was marginally associated with systemic exogenous hormonal contraception.25 Menopausal hormonal changes are probably associated with disease manifestation in a fraction of patients.25 Further research is needed in order to characterise an interaction between hormonal changes and immune response in NMOSD. Brainstem NMOSD lesions can cause diencephalic syndromes and hypothalamus dysfunction, which can occasionally give rise to endocrinopathies with secondary amenorrhea.

Fertility and menopause
Regarding the effect of NMOSD on fertility of women, there is almost no human data. The expression of nine aquaporin (AQP) isoforms (AQP1–AQP9) has been confirmed in the female reproductive tract and can be detected in the uterus, cervix, ovaries and vagina of adult mammals.26 It has also been shown that expression of various AQPs can be regulated by steroid sex hormones.27 In the CNS, AQP4 is highly expressed in periventricular areas and in the paraventricular hypothalamic nucleus involved in regulation of gonadotropin-releasing hormone (GnRH) neurons.28 These findings suggest that AQP4 antibodies can potentially affect reproductive function in females. Interestingly, in an experiment, AQP4-deficiency induced subfertility in female mice.29 The level of the anti-Mullerian hormone (AMH), as an indicator of ovarian reserve and function, is probably reduced in women with NMOSD.30
Interestingly, lower AMH levels were also associated with disease activity but not with any type of treatment. Despite being used rarely nowadays in NMOSD, aggressive immunosuppressive medications, such as cyclophosphamid or mitoxantrone, also reduce ovarian reserve and fertility and should be generally avoided in young patients.

**Pregnancy and postpartum period**

**Maternal disease activity.** Sex hormones, mostly oestrogen but also progesterone and testosterone, have an effect on immune function, both quantitatively and qualitatively.\(^{31-34}\) It is well known that pregnancy can change the course of autoimmune diseases. In general, it stabilises Th1-related diseases like rheumatoid arthritis and MS, but causes exacerbation of Th2-related disease like systemic lupus erythematosus. There is a growing data pointing out that pregnancy affects the disease course of NMOSD. Current data suggest that the risk for postpartum relapse is increased in women with NMOSD, especially in the first 3–6 months after delivery, and that these relapses are associated with an increase in expanded disability status scale (EDSS).\(^{35-39}\) Due to cessation of immunotherapy, the relapse risk might also be increased during the first trimester of pregnancy.\(^{39}\) Interestingly, more women than expected were first diagnosed with NMOSD during the first 3 months postpartum.

**Pregnancy outcomes.** Women with NMOSD have an increased risk of negative pregnancy outcomes.\(^{40}\) Pregnancies after NMOSD onset were associated with a significantly increased risk of miscarriage (independent of the risk associated with advanced maternal age). Moreover, miscarriages were found to be associated with disease activity in the preconception and intrapregnancy period.\(^{40}\) Prevalence of preeclampsia is also increased in women with other autoimmune diseases or a history of miscarriage. Increased miscarriage in NMOSD could be explained by the presence of AQP4 expression in placenta. Placental AQP4 expression is high during the second trimester and then decreases progressively through to the end of pregnancy.\(^{41}\) Placental AQP4 expression could theoretically contribute to adverse pregnancy events. In one case report, the placenta from a woman with NMOSD contained regions of necrosis and complement deposition mostly in perivascular areas of syncytiotrophoblasts.\(^{42}\) Comprehensive investigations of placentas from pregnancies in NMOSD are needed to understand the role of local AQP4 expression and its relationship with complications.

**Maintenance immunosuppressive therapy during pregnancy.** Due to the severity of NMOSD relapses, pregnancy-related suspension of medication might put patients at risk of increasing disability. Therefore, pregnancies should be planned and patients counselled carefully. Treatment with immunosuppressants, like methotrexate, mycophenolate mofetil and mitoxantrone, are not recommended during pregnancy due to their teratogenic potential and risk of miscarriage, and have to be stopped prior to pregnancy.\(^{43-45}\) Alternatives might be to continue the medication with azathioprine during pregnancy or conception shortly after the last rituximab infusion.\(^{33,44}\) Low-dose prednisolone and monthly intravenous immunoglobulin (IVIG) are also considered safe during pregnancy. More data are needed for newer medications shown to be beneficial in clinical trials; however, promising experience is already available for eculizumab from paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome, or haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome during pregnancy.\(^{36}\) Disabling relapses can be treated with corticosteroids during pregnancy, plasma exchange is an alternative option in steroid refractory or severe attacks and should be started in the latter case without delay.\(^{45,47}\) A recently published review gives a comprehensive overview about the safety data of immunotherapies used in NMOSD during pregnancy and lactation.\(^{44}\)

**Conclusion**

Existing data suggest that pregnancy and NMOSD can have a negative effect on each other.\(^{44}\) This may indicate that better understanding of immunologic changes occurring during pregnancy may provide additional information about the immunopathogenesis of NMOSD. Taking attack severity into account, continuation of selected immunotherapies close to the start of, or even during, pregnancy might be justified in individual cases.

**Autoimmune encephalitis**

**General introduction**

AE by itself describes a heterogeneous group of diseases affecting all age groups and both
genders, occurring without and with underlying tumour (paraneoplastic), post-infectious and idiopathic, differing in pathomechanism/pathogenesis of disease, sometimes with strong genetic predisposition and with response to therapy ranging from excellent to negligible.

More homogeneous subgroups are definable by classification by type of underlying antineuronal antibody. Different antineuronal antibodies are often associated with distinct clinical syndromes, age spectra, sex predominance, tumour associations (type and frequency), therapy responsiveness and prognosis. While seronegative AE exists and is a relevant clinical issue, this subsection will concentrate on encephalitis forms defined by antibodies. In the following, the most common forms of AE are described in order of their relative prevalence and with a focus on gender aspects.

Epidemiology focusing on gender aspects

Anti-N-methyl-D-aspartate receptor encephalitis. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is responsible for up to 40% of all seropositive AE syndromes. This syndrome starts with behavioural abnormalities and memory dysfunction and eventually leads to seizures, loss of consciousness and orofacial dyskinesias. In a series of 577 patients (81% female), the median age was 21 years, 37% were younger than 18 years and 5% older than 45. Female preponderance (88%) was especially marked between puberty and menopause. Sex differences were less obvious in age groups below 12 years (males 39%) and above 45 (males 43%). Of note, tumour association (53%) was highest in women between 12 and 45 years (women <12 years 6%, >45 years 25%) whereas in men tumour association increased with age (<12 years 0%, 12–45 years 7%, >45 years 25%). Most tumours were ovarian or extravarian teratomas (96%), which in part explains the gender and age distribution, with ovarian teratomas being the most common ovarian tumour in the age group between 12 and 45 years. However, even in non-tumour cases of anti-NMDA receptor encephalitis, women in this age group are significantly more often affected than men (female to male ratio 3.6:1). Since paraneoplastic anti-NMDA receptor encephalitis in most cases has a favourable outcome, fewer relapses after early treatment of teratoma and does not benefit from further ‘second line’ immunosuppression, these women have a different treatment approach from patients with non-paraneoplastic variants.

Anti-LGI1-encephalitis. Anti-leucin-rich-glioma-inhibited 1-(LGI1) encephalitis is assumed to be the second most common AE form. Patients have a subacute/chronic presentation with memory dysfunction, behavioural abnormalities/personality changes and seizures. Older patients (median age 64 years (range 31–84) with a slight male preponderance are usually affected. Interestingly, LGI1-encephalitis has one of the strongest genetic predispositions observed so far in autoimmune syndromes. Almost 90% of all affected patients are homozygous or heterozygous carriers of the HLA-DRB1*07:01 and associated haplotypes.

Furthermore, autoantibodies in LGI1-encephalitis are usually of the IgG4 subclass – an observation made in several autoimmunopathies, many of which have a genetic predisposition. However, this genetic predisposition is not different between genders.

Anti-CASPR2-encephalitis. Anti-contactin-associated-protein-2 (CASPR2) encephalitis usually has core symptoms of limbic encephalitis (personality changes/psychiatric symptoms, memory dysfunction, epileptic seizures and sometimes autonomous dysfunction). In most cases, additional syndromes, for example, ataxia or pain syndromes are associated and together form CASPR2-spectrum disorder, which usually manifests in older patients (median age 66 years, range 25–77) with striking male predominance. Similar to anti-LGI1 encephalitis, anti-CASPR2 encephalitis has been shown to be associated with non-complement fixing antibodies of the IgG4 subclass and to have a strong genetic predisposition, being highly associated with distinct HLA class II haplotypes (HLA-DR). It is intriguing to speculate that the strong genetic background of these AEs might be associated with the male predominance.

Anti-GAD encephalitis. High-titre antibodies against glutamic acid decarboxylase (GAD) associate not only with limbic encephalitis, but also cerebellar dysfunction, stiff-person syndrome or pure temporal lobe epilepsy and sometimes combinations thereof. Neurologic anti-GAD autoimmunity usually manifests in the second to fourth decade of life and has a strong female predominance.
Other AE subtypes. Other AE subtypes mostly have a slight female preponderance or equal gender ratios (Table 1). AE associated with antibodies targeting intracellular antigens are considerably less common than, for example, anti-NMDA receptor encephalitis or anti-LGI1 encephalitis. They occur with a very strong tumour association, resulting in over 95% of patients having (sometimes occult) carcinomas of neuroendocrine origin, most commonly small cell lung cancer (SCLC). Anti-Hu encephalomyelitis affects males more often than females, presumably because of higher incidence of SCLC in men due to tobacco usage. More recently, novel tumour therapy using immune therapies, specifically check-point inhibitor therapy, has been observed to cause seronegative and seropositive AE as a complication. Gender ratios have not been reported for these rare associations.

Besides the previously discussed gender predominance in some forms of AE, no clear gender association exists concerning response to therapy after exclusion of confounding effects of tumour therapy, relapse rate and disease severity. However, numbers are too small to firmly exclude further small-scale gender related differences. This question will need to be addressed in large registries and joint international analyses.

### Table 1. Female to male ratios in autoimmune encephalitis subtypes.50,61,65,66

<table>
<thead>
<tr>
<th>Encephalitis Type</th>
<th>Median Age of Manifestation (Range)</th>
<th>Female to Male Ratio</th>
<th>Tumour Association</th>
<th>Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-NMDA receptor encephalitis</td>
<td>21 (0.2–85)</td>
<td>9:1</td>
<td>25–50% ovarian teratomas</td>
<td>Mostly good</td>
</tr>
<tr>
<td>Anti-LGI1-encephalitis</td>
<td>64 (31–84)</td>
<td>1:1.6–1.9</td>
<td>Rare</td>
<td>Initially, mostly good, residual cognitive syndrome not uncommon</td>
</tr>
<tr>
<td>Anti-CASPR2 encephalitis</td>
<td>66 (25–77)</td>
<td>1:9</td>
<td>Rare, in Morvan-syndrome up to 20% thyromomas</td>
<td>Mostly good</td>
</tr>
<tr>
<td>Anti-GAD encephalitis/ temporal lobe epilepsy syndrome</td>
<td>26 (12–49)/32 (9–67)</td>
<td>9:1</td>
<td>Rare</td>
<td>Often insufficient, especially epileptic seizures do not respond well</td>
</tr>
<tr>
<td>Anti-AMPA receptor encephalitis</td>
<td>56 (23–81)</td>
<td>2.3:1</td>
<td>Common, SCLC</td>
<td>Good, especially in idiopathic forms</td>
</tr>
<tr>
<td>Anti-GABA(B) receptor encephalitis</td>
<td>61 (16–77)</td>
<td>1:1.5</td>
<td>Common, SCLC</td>
<td>Good, especially in idiopathic forms</td>
</tr>
<tr>
<td>Anti-GABA(A) receptor encephalitis</td>
<td>40 (0–88)</td>
<td>1:1</td>
<td>Rare</td>
<td>Good</td>
</tr>
<tr>
<td>Anti-DPPX encephalitis</td>
<td>52 (13–76)</td>
<td>1:2.3</td>
<td>Unknown</td>
<td>Good</td>
</tr>
<tr>
<td>Anti-mGluR5 encephalitis</td>
<td>29 (6–75)</td>
<td>1:1</td>
<td>Common, lymphoma</td>
<td>Good, especially in idiopathic forms</td>
</tr>
<tr>
<td>Anti-IgLON5 encephalitis</td>
<td>64 (46–83)</td>
<td>1:1</td>
<td>Rare</td>
<td>Limited</td>
</tr>
<tr>
<td>Anti-Hu</td>
<td>63 (28–82)</td>
<td>1:3</td>
<td>Common, SCLC, other neuroendocrine tumours</td>
<td>Limited</td>
</tr>
</tbody>
</table>

SCLC, small cell lung cancer.

**Fertility and menopause**

Determination of fertility in women during AE or following AE has not been examined systematically, but clinical experience does not give any indication of reduced fertility due to direct immunological disease mechanisms. However, neurologic residual symptoms, complications of intensive care or immunotherapy and secondary
socioeconomic factors like partnership and financial situation in chronic diseases all contribute to the possibility of reduced conception rates. No systematic study has addressed premature menopause in women affected by AE in general. Personal experience of the authors does not indicate an increased incidence of early menopause but systematic evidence is missing.

Of all AE patients, patients with anti-NMDA receptor encephalitis and GAD autoimmunity are commonly affected in reproductive age. In the remaining AE subtypes, age of manifestation is usually post-menopausal. The authors’ experience indicates that, post-NMDA receptor encephalitis, women often restart or continue family planning, most likely because most women have a monophasic, albeit sometimes protracted, course. In contrast, GAD autoimmunity often leads to chronic disease and seizure disorder. That might be the reason why – in the authors’ experience – women with GAD autoimmunity less often become pregnant.

In general, all immunosuppressive drugs carry the potential risk of reduced fertility and teratogenicity. During any immunosuppression other than IVIG, patients must be counselled for the need of contraception. However, steroids (non-high-dose), azathioprine and rituximab appear to have, at most, limited effects on fertility or teratogenicity (reviewed in Leroy et al.67). Furthermore, in anti-NMDA receptor encephalitis, teratomas cause the disease in 25–50% of cases and sometimes unilateral oophorectomy needs to be performed, which might influence future fertility due to any pathologies affecting the second ovary.51

Pregnancy and postpartum period
Several cases have been reported where patients developed anti-NMDA receptor encephalitis during pregnancy or became pregnant after recovery. In general, there is currently no conclusive evidence suggesting increased rates of teratogenicity or infant development delay in patients who had anti-NMDA receptor encephalitis during pregnancy or who became pregnant after recovery from the disease. There appears to be a higher incidence of preterm delivery (up to 50%), which is most likely due to intensive care treatment and obstetric decisions based on the neurological condition of the mother.

The latest case series reports six pregnant patients with anti-NMDA receptor encephalitis occurring in early and late pregnancy.68 Five additional pregnant women (median 5 months, range 1–42 months) after a prior episode of anti-NMDA receptor encephalitis were reported.68 Median age in this series was 23 years (range 19–37 years). No obstetric complications were reported, yet caesarean sections were done in 36% of patients due to the neurological condition of the mother. Only 1 out of 11 newborns had temporary and quickly reversible respiratory distress, likely due to anticonvulsive medication administered to the mother. The remaining 10 newborns showed no abnormalities after delivery. In one of these healthy newborn babies, NMDA receptor antibodies were tested and could be detected. In nine infants (including the baby who had detectable NMDA receptor antibodies) with available follow up (median 18 months, range 7–96), no developmental delays or behavioural abnormalities were observed.

Around 20 other cases were reported non-systematically in the literature.69–85 Their analysis largely confirms these findings, although up to one-third had complicated pregnancies or spontaneous miscarriages, most likely due to intensive care treatment, epileptic seizures and autonomous dysfunction of the mothers. There is a report on one child with developmental delay and epilepsy due to cortical dysplasia, born to a mother with anti-NMDA receptor encephalitis starting at gestational week 7, who later died from septic shock.78 Multiple complications, uteroplacental insufficiency and delivery at gestational age 34 weeks most likely contributed to cortical dysplasia. Another child, whose mother developed anti-NMDA receptor encephalitis in gestational week 37, died of diffuse brain oedema 3 weeks after delivery.71 Placental anti-NMDA receptor antibody transfer was hypothesised to be the cause. Besides those two cases, a further 10 reported children for whom follow up was available (median age 12 years, range 6–36) showed normal development.

Most patients received immunotherapy, including rituximab, during pregnancy and in one case even cyclophosphamide, sometimes in combination with plasma exchange. This was well tolerated and not associated with complications. Most experts agree that the risk of untreated
anti-NMDA receptor encephalitis with seizures, intensive care complications and autonomic dysfunction far outweighs the risk associated with immunotherapy including rituximab. An ovarian teratoma was detected and removed in around half of the reported patients during pregnancy. A recent preclinical animal study has suggested that passive transfer of monoclonal anti-NMDA receptor antibodies to pregnant mice resulted in developmental abnormalities. This study represents an animal model with very limited applicability to patients.

In another study, patients with postpartum psychosis but no clear encephalitis episode were screened for neuronal autoantibodies. In 4 out of 96 cases, autoantibodies targeting extracellular neuronal antigens were identified. In two patients, antibodies against NMDA receptors were detected using cell-based assay, in the remaining two cases the target antigen could not be identified after testing for all known antineuronal antibodies. Notably, seropositive patients showed no clinical characteristics allowing to separate them from the seronegative group and did not require immunotherapy due to good symptom control under antipsychotic therapy. In contrast, several cases with severe autoimmune anti-NMDA receptor encephalitis have been reported that were initially misdiagnosed as postpartum psychosis due to primary manifestation with psychiatric symptoms, followed by recurring seizures, hyperventilation and intensive care treatment.

In summary, the authors suggest, based on their own experience and publications, that pregnant women during or after anti-NMDA receptor encephalitis and their relatives should be counselled that (1) there is no clear evidence of a direct immune mediated effect on foetal development and thus no indication for abortion; (2) due to intensive care treatment, seizures and possible autonomic dysfunction, the pregnancy should be considered high risk and closely monitored for signs of foetal distress; and (3) danger to the unborn child due to these complications of AE presumably outweighs possible side effects of anti-convulsive and immunosuppressive medication and these should not be withheld. Anti-NMDA receptor encephalitis should be considered in patients with post-partum psychosis as a rare but treatable differential diagnosis.

Conclusion

Many autoimmune encephalitis subtypes have a gender predominance: in some subtypes, women are more frequently affected (anti-NMDA receptor encephalitis, anti-GAD autoimmunity) and, in others, a male (CASPR2-autoimmunity) predominance has been observed. This is due, in part, to gender-related tumour incidence. Tumour-treatment related differences exist between sexes, for example, ovarian-teratoma associated anti-NMDA receptor encephalitis only occurs in women, they tend to have fewer relapses and better outcomes if diagnosed and treated in time compared with non-teratoma associated cases in men and women. No other clearly sex-related differences in presentation, treatment response and outcome are currently recognised, yet numbers are still too small to rule these out completely.

Anti-GAD autoimmune syndromes and anti-NMDA receptor encephalitis occur mainly in reproductive age. Fertility is presumably not directly affected by immune-mediated mechanisms in autoimmune encephalitis, yet other factors like chronicity of disease and immunotherapy might influence fertility.

Most cases of pregnancy during or after AE were reported in patients with anti-NMDA receptor encephalitis. High-risk pregnancies and premature delivery occur mostly due to neurological symptoms in women with acute anti-NMDA receptor encephalitis. However, teratogenicity and developmental delay in children has not been shown unequivocally. Nevertheless, systematic follow up of children born to mothers during or after AE would help further clarify the situation.

**Myasthenia gravis and Lambert-Eaton myasthenic syndrome and pregnancy**

**General introduction**

Two different types of autoimmune diseases affect the neuromuscular synapse, leading to impaired/disturbed neuromuscular transmission: autoimmune MG, caused by autoantibodies to acetylcholine receptor (AChR), muscle tyrosine kinase (MuSK) or lipoprotein-receptor-like protein type 4 (LRP4); and LEMS, an autoimmune disorder with autoantibodies directed against presynaptic calcium channels leading to reduced release of acetylcholine (ACh) vesicles and...
thereby to impaired neuromuscular transmission. Both diseases affect young women in the reproductive phase. In this part of the review we focus on gender-specific considerations for MG and LEMS with a main focus on planning a pregnancy in women with MG.

Epidemiology focusing on gender aspects
In autoimmune MG, epidemiological data show an age-related gender distribution: whereas MG is more frequent in women up to 50 years than in men, with a ratio of 1.6:1.0, late onset and very late onset MG show a predominance of male versus female patients, with a ratio of 1.65:1.0 as shown in a very recent study. In autoimmune LEMS, women and men are rather equally affected, whereas in LEMS associated with cancer, mainly small cell lung cancer, up to 70% of patients are male and older than 60 years. Remission appeared to be more likely in early onset MG, but was not shown to be related to gender. In young patients, in particular in women, MG frequently goes along with other autoimmune diseases like autoimmune thyroid disease, rheumatoid arthritis, colitis and others, which may influence treatment modalities and physical preconditions with regard to conception and to the course of pregnancy as well as to treatment of MG during pregnancy.

Fertility and menopause
Fertility does not seem to be primarily affected in MG or LEMS, but may be reduced after due to treatment with cyclophosphamide in both women and men. Male fertility may also be reduced by cyclosporine A or tacrolimus medication due to reduced spermatogenesis and disturbed maturation of sperms. Mycophenolat mofetil (MMF) does not seem to have negative effects on fertility in both sexes. Methotrexate (MTX) may reduce the number of sperm in men.

There are no data correlating disease course of MG and LEMS and the menopausal hormonal status, although there is evidence that hormones influence the immune system and vice versa.

Pregnancy and post-partum period
Preconditions for pregnancy. The recommendations for pregnancy in MG proposed by a consortium of the Myasthenia Gravis Federation of America (MGFA) include planning for pregnancy, multidisciplinary communication, and disease under good control. It is recommended to postpone thymectomy. According to our personal experience/in our clinical practice, uncontrolled MG with marked fluctuations and bulbar or respiratory symptoms, the regular need for steroids >20 mg, lack of compliance and adequate self-management may be negative preconditions regarding management of pregnancy (personal communication).

While oral pyridostigmine in low-to-moderate doses of up to about 180 mg per day is the first line symptomatic treatment, higher doses of acetylcholine esterase inhibitors, in particular in the case of intravenous application, may cause uterine contractions (personal communication). Prednisone is the immunosuppressive agent of choice during pregnancy. Azathioprine or cyclosporine are classified as relatively safe. Mycophenolat mofetil, cyclophosphamide and MTX are known teratogens and have to be stopped prior to pregnancy or in case of accidental exposure. Medication should be switched to a combination of pyridostigmine alone or, if necessary, in combination with steroids up to 20 mg. Severe fluctuations or deterioration of MG should be treated with IVIG up to 1 g/kg body weight or plasma exchange. Rituximab given before onset of pregnancy does not seem to have negative influences. The patient should be under supervision of experienced neurologists and gynaecologists, and the patient should be compliant.

After childbirth, possible deterioration of MG as shown in the following paragraph has to be considered in decisions on further therapeutic strategies. Maternal disease activity. Pregnancy may influence the course of MG and LEMS by for example, hormonal factors. The effects of pregnancy on the disease course of MG and LEMS are not predictable. Table 2 gives an overview of several studies. According to a study from the Netherlands the risk of being diagnosed with MG was higher in the postpartum period, whereas according to a Norwegian study it was equally distributed during and after pregnancy.

Ducci et al. reported deterioration of MG in about 50% of pregnancies (n = 30), in particular in the 2nd trimester in patients with lower myasthenia...
gravis composite (MGC), and in patients with abnormal repetitive nerve stimulation. No change of clinical myasthenic symptoms was found in patients with longer disease duration and normal repetitive nerve stimulation. In contrast, improvement of MG during pregnancy was seen in patients with higher MGC scores.

Batocchi et al. observed deterioration of symptomatic MG during pregnancy in 19% (6/31) versus improvement in 39% (12/31). Postpartum deterioration occurred in 15 of 54 pregnancies (28%) in symptomatic (n = 31) but also in previously asymptomatic (n = 23) MG patients. Deterioration of MG during pregnancy occurred in 11 of 27 (40%) retrospectively evaluated pregnancies from Turkey, which is in accordance with previous data from Mexico.

A retrospective study on 17 MUSK-ab positive women with 27 pregnancies either after MG onset, after an average 9.7 years of disease duration (n = 4) or 17 years before disease onset (n = 23) revealed no relapse 12 months after delivery, no pre-eclampsia, stillbirths or birth defects in both groups. One case of transient neonatal myasthenic syndrome occurred in the group of patients with MG onset before pregnancy.

Iatrogenic deterioration of muscle weakness in MG/LEMS in the course of pregnancy may be caused by parenteral application of high-dose magnesium for preeclampsia and premature contractions.

**Pregnancy outcomes.** Rarely, in AChR antibody positive MG, arthrogryposis with joint contractures and muscle dysmorphia or the more complex foetal AChR inactivation syndrome (FARIS) may develop, the latter in about 4% of cases (see Table 2).

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
</tr>
</tbody>
</table>
| Deterioration during pregnancy | 0-50% [Ducci et al.; Batocchi et al.; Tanacan et al.; Tellez-Zenteno et al.; Santos et al.; Hoff et al.]
| Deterioration after pregnancy | 0% [Santos et al.; 11% [Boldingh et al.]; 28% [Batocchi et al.]]
| Deterioration by interventions | Single case reports
| Increased risk for onset of MG | 11% [Boldingh et al.]
| EPH gestosis | 0-3% [Hoff et al.]
| Preterm rupture of amniotic membranes | 5%; 5.5% [Hoff et al.; Hoff et al.]; 14.8% [Tanacan et al.]
| Delivery            |              |
| Increased rate of caesarean section | 17%; 17.3% [Hoff et al.; Hoff et al.]; 30% [Batocchi et al.]; 78% [Tanacan et al.]
| Increased rate of interventions during delivery | 40%; 41.5% [Hoff et al.; Hoff et al.]
| Foetus/newborn      |              |
| Foetal distress syndrome | 19% [Hoff et al.]
| Lower gestational age at birth | 3% [Hoff et al.]
| Lower weight/length at birth | 3.9% [Hoff et al.]
| Anomalies (not defined) | Single case reports [Hakohen et al.]
| Arthrogryposis/FARIS | Single case reports [Hakohen et al.]
| Neonatal MG/LEMS    | 2% [Tellez-Zenteno et al.]; 12.9% [Ducci et al.]; 19.2% [Hoff et al.]

AChR, acetylcholine receptor; EPH, oedema proteinuria hypertension; FARIS, foetal AChR inactivation syndrome; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis.
muscle hypotonia, suckling weakness, dysphagia, respiratory insufficiency due to lung hypoplasia, persistent bulbar symptoms, facial diplegia, CNS malformations and undescended testicles. In most of these cases, bulbar and skeletal muscle symptoms and lung dysplasia persist over years. Bulbar and skeletal muscle symptoms may improve under physiotherapy and medication with pyridostigmine and salbutamol. In MG, mothers who have given birth to a child with arthrogryposis or FARIS should be treated regularly with IVIG or plasma exchange during the next pregnancy since there is a great risk for the occurrence of arthrogryposis or FARIS in future pregnancies. In LEMS, foetal arthrogryposis has not been described so far.

**Neonatal MG and LEMS.** Transfer of maternal antibodies relevant for neuromuscular transmission (AChR, MuSK, antibodies directed against voltage-gated calcium channels) via placenta starts from gestational week 13 and is enhanced during delivery. This may cause neonatal myasthenic syndrome in AChR-antibody positive MG in MuSK-antibody-positive MG and also in LEMS. A single case of neonatal myasthenic syndrome in the newborn of a mother with localised (ocular) seronegative MG has been reported. Antibodies against AChR, MuSK and LRP4 were shown to be detectable in the newborn’s circulation with and without neonatal MG. Thus, distinct factors like binding affinity to the foetal type of AChR seem to determine whether neonatal myasthenic symptoms occur or not. Hoff et al. found that the risk of neonatal MG was halved in mothers who had undergone thymectomy, and that children with neonatal MG were more likely to show signs of foetal distress during delivery. Neonatal MG usually lasts for about 8–14 days, with the first symptoms mostly occurring within the first 24 h after birth. The severity of neonatal MG does not correlate with the severity of MG in the mother. Rarely, artificial ventilation is necessary. Some support with breastfeeding in the case of poor suckling, and low doses of acetycholine esterase inhibitors are sufficient in most cases. Ducci et al. found neonatal MG in 12.9% of 30 pregnancies without distinct predictors. Tellez-Zenteno reported only one case of neonatal MG in 18 pregnancies.

**Obstetric outcomes.** Vaginal delivery is possible in stable MG and LEMS, but elective caesarean section is performed frequently to minimise risks for mother and the newborn(s), and was two times higher in the retrospective study by Hoff and coworkers. They also found that women with MG had a higher rate of complications at delivery compared with mothers without MG (40.9% versus 32.9%, p = 0.05) with the risk for preterm rupture of amniotic membranes three times higher in the MG group. Severe anomalies were seen in 5 of 127 children (3.9%) and death occurred in 3 children. In another retrospective study, obstetric complications occurred in 20 of 35 pregnancies. Premature rupture of membrane and caesarean section were most common. In a retrospective study from Turkey comprising 27 pregnancies, there were 4 miscarriages, 3 preterm births, and 4 cases of premature rupture of membranes with a higher rate of these complications, as well as a higher rate of Caesarean sections, lower gestational age at birth, lower birth weight and 5-min Apgar score in patients with deteriorating MG (11/27; 40.7%).

**Breastfeeding.** Breastfeeding and the risk of transfer of pathogenic antibodies has been controversially discussed, but it could be shown that colostrum and milk contain only about 2% of the mothers’ IgG serum levels. Thus, AChR ab may be transferred in part by breastfeeding but not to a relevant extent. For many positive reasons breastfeeding is recommended also for newborns with transient neonatal MG or arthrogryposis or FARIS. High doses of pyridostigmine taken by breastfeeding mothers may rarely lead to increased bowel movement in the newborn. Not only during pregnancy but also during breastfeeding the application of MMF, MTX and cyclophosphamide is not recommended. Whether stimulation of prolactin secretion by breastfeeding may provoke negative immunological effects due to the cytokine-like capacities of prolactin is unclear so far.

**Special aspects of males.** Apart from the administration of drugs influencing fertility there are no special reproductive recommendations in male patients suffering from MG or LEMS.

**Conclusion**
In both MG and LEMS, young women are particularly affected. Therefore, there are peculiar questions and aspects regarding pregnancy and the postpartum period which have to be dealt
Box 1. Recommendations for women with NMOSD, AE or MG/LEMS before, during and after pregnancy.

**General recommendations**
- Pregnancies in women with NMOSD, AE or MG/LEMS should be considered high risk.
- A pregnancy should be preceded by careful planning, multidisciplinary communication and if possible controlled disease activity.
- Methotrexate, mycophenolate mofetil, mitoxantrone and cyclophosphamide have to be discontinued before conception and in any case of accidental exposure during pregnancy.
- Rituximab shortly before conception can be an option for women with various neuroimmunological diseases
- Eculizumab can be an option during pregnancy in severe NMOSD or MG
- Breastfeeding is possible under steroids, Azathioprine, IVIG and monoclonal antibody treatment
- Include women in pregnancy registries if possible

**Special recommendations depending on disease**

**NMOSD**
- A potentially increased relapse risk during the first trimester of pregnancy has to be kept in mind if immunotherapy is stopped.
- Relapses during pregnancy can be treated with corticosteroids or plasma exchange.
- Therapy options during pregnancy include azathioprine, low-dose prednisolone and monthly IVIG.
- Depending on disease severity continuation of azathioprine during pregnancy, or conception shortly after the last rituximab administration can be considered.
- While planning postpartum treatment, the elevated relapse risk in the first 3–6 months after delivery has to be kept in mind.

**AE**
- Immunosuppressive treatment options include IVIG, corticosteroids and azathioprine during pregnancy, as well as rituximab administration (shortly) before conception.

**MG/LEMS**
- Thymectomy should be postponed in MG patients seeking pregnancy.
- Prior conception treatment should be switched to pyridostigmine or a combination of pyridostigmine and low-dose corticosteroids. Alternatively, rituximab administration before onset of pregnancy can be considered.
- During pregnancy low-dose prednisone is the treatment of choice. Treatment with azathioprine or cyclosporine can also be considered.
- In case of severe fluctuations or deteriorations during pregnancy IVIG should be administered.
- Vaginal delivery is possible in stable patients.
- In case of neonatal myasthenic syndrome low doses of acetylcholine esterase inhibitors and if necessary support with breastfeeding are mostly sufficient.
- After delivery possible deterioration of disease activity has to be considered.

AE, autoimmune encephalitis; IVIG, intravenous immunoglobulin; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder.

with, thus, there is a need for/particular advice and guidelines are required (see Box 1). Pregnancy may influence disease course and in rare cases also foetal development in MG. The course of MG during pregnancy is unpredictable. Worsening of MG after delivery has to be borne in mind. Transient neonatal myasthenic symptoms may occur in MG and LEMS and may be responsible for foetal distress during delivery. In addition, immunosuppressive therapy and the severity of MG/LEMS may limit fertility and physical conditions during and after pregnancy in young women.

**Conflict of interest statement**
Ayse Altintas has received speaker honoraria for non-promotional education events and travel grants from Merck, TEVA and Novartis. Christiane Schneider-Gold has received consulting and speaker’s honoraria from Alexion Pharmaceuticals, Amicus Therapeutics, Bayer Schering, CSL Behring, Grünenthal, Lupin Pharmaceuticals and TEVA. Andrea I. Ciplea has received speaker honoraria from Bayer Healthcare and travel grants from Sanofi Genzyme, Teva and Novartis. Frank Leyboldt discloses receiving speaker honoraria from Biogen, Roche, Merck, Fresenius, Teva, Bayer, Novartis, Alexion and advisory board memberships Roche, Biogen and Alexion. Kerstin Hellwig has received travel grants from Biogen, Novartis and Merck; received speaker and research honoraria from Biogen Idec Germany, Teva, Sanofi Genzyme, Novartis, Bayer Healthcare, Merck Serono and Roche. Frank Leyboldt, Klaus-Peter Wandinger, Justina Dargvainiene and Ralf Junker disclose working for an academic institution offering commercial antibody testing.
Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Part of this study was supported by the German Ministry of Education and Research (BMBF, 01GM1908A, Frank Leypoldt).

ORCID iD
Kerstin Hellwig https://orcid.org/0000-0003-4467-9011

References


21. Wingerchuk DM, Hogancamp WF, O’Brien PC, et al. The clinical course of neuromyelitis...


49. Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the


