

Pregnancy outcomes in anti-NMDA receptor encephalitis

Case series

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Abstract

Objective

To report the effects of anti-NMDA receptor (NMDAR) encephalitis in pregnant patients and their babies.

Methods

We studied a retrospective cohort of patients who developed anti-NMDAR encephalitis during pregnancy or became pregnant while recovering from the encephalitis. In addition, we reviewed the English literature between 2010 and 2019 related to this topic.

Results

We studied 11 patients; 6 developed anti-NMDAR encephalitis during pregnancy, and 5 became pregnant while recovering. There were no obstetrical complications, but 6 (55%) babies were premature. Ten newborns were healthy, and 1 (9%) developed transient respiratory distress. Nine infants had assessable follow-up (median 18 months; range, 7–96 months), and all showed normal development. We identified 21 cases in the English literature. Obstetrical complications occurred in 7 (33%) pregnancies. Two patients died of septic shock (1 baby successfully delivered), another 2 had miscarriages, and in 2, the pregnancy was terminated. Sixteen babies (76%) were delivered, 9 (56%) premature. At birth, 13/16 (81%) newborns were healthy, 2/16 (13%) had transient neurologic or respiratory symptoms, and 1 (6%) died of brain edema. Follow-up (median 12 months; range, 6–36 months) was reported for 8 children: 7 (88%) showed normal development and behavior, and 1 (13%) cortical dysplasia. Immunotherapy was used during pregnancy in 7 (64%) of our patients and 18 (86%) of the reported cases, including rituximab in 4 cases, without adverse effects.

Conclusions

Patients who develop anti-NMDAR encephalitis during pregnancy or become pregnant during recovery often have obstetrical complications, but most of the newborns are healthy and appear to have normal development.

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Glossary

IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NMDAR = NMDA receptor.

Anti-NMDA receptor (NMDAR) encephalitis is a severe but treatable autoimmune neurologic disease that often results in psychotic symptoms, seizures, dyskinesias, decreased level of consciousness, dysautonomia, or central hypoventilation.¹ About 60% of patients are young women, and some develop the disease during pregnancy.^{1,2} Several reports have suggested that dysautonomia, seizures, or central hypoventilation play important roles in the potential complications that pregnant patients may develop.^{3–7} Other studies proposed that transplacental transfer of NMDAR antibodies can result in acute encephalopathy or death of the newborn or eventually result in autistic-spectrum disorders.^{3,8–10} In a study based in an experimental animal model of transplacental transfer of a human monoclonal NMDAR antibody, Jurek et al.¹¹ suggested that antibodies of asymptomatic seropositive pregnant women (without evidence of anti-NMDAR encephalitis) caused developmental and cognitive deficits in the offspring. However, the authors did not provide any experimental evidence that the antibodies from asymptomatic mothers of children with cognitive or neurodevelopmental deficits were pathogenic. The best human model to examine the postulate of these authors is pregnant patients with anti-NMDAR encephalitis who all have clear evidence of pathogenic NMDAR antibodies. In fact, the experience and number of reports on pregnant patients with this disease are limited, and the effects of the immune response on patients and offspring are largely unknown. Here, we report 11 new patients and review 21 previously reported cases, describing the effects of the disease on the mothers and babies and the treatments used and outcome.

Methods

Data collection

Patients whose serum or CSF were examined for NMDAR antibodies in 3 referral centers (Barcelona, Spain; Lyon, France; and Kiel/Lübeck, Germany) and who were pregnant when they developed anti-NMDAR encephalitis or became pregnant while recovering from the disease were included in the study. Clinical information was retrospectively provided by the treating physicians, patients, and families using a structured questionnaire. We focused on the age and neurologic symptoms of the mothers, presence of an underlying tumor, immunotherapies used during pregnancy, duration of the pregnancy, and type of delivery. Mothers' neurologic outcomes were assessed using the modified Rankin Scale (mRS).¹² The short-term outcomes of the infants were obtained from records of obstetricians or midwives and the APGAR score 5 minutes after delivery. We reviewed whether the babies were later found to have developmental problems or alterations of behavior and social interaction.

Literature search

Previously reported cases were identified through MEDLINE search using the following keywords: “NMDAR,” “N-methyl-D-aspartate,” “antibodies,” “autoimmune encephalitis,” and “pregnancy,” published between January 1, 2010, and August 15, 2019.

Standard protocol approvals, registrations, and patient consents

We obtained written informed consent from all patients. The study was approved by the local institutional review boards of Hospices Civils de Lyon (CPP SUD-EST II, US registration number 11263) and Hospital Clínic de Barcelona (registration number HCB/2018/0192). All data are available on request at Neuroimmunology Program, IDIBAPS Institute, Barcelona (Spain).

Data availability

Any data not published within the article are available and will be shared anonymously by request from any qualified investigator.

Results

Patients of the current series

We retrospectively assessed the information of 11 cases, including 6 patients (55%) who developed anti-NMDAR encephalitis during pregnancy (3 in the 1st trimester, 2 in the 2nd trimester, and 1 in the 3rd trimester), and 5 (45%) who became pregnant during recovery (median time from onset of recovery: 5 months [range, 1–42 months]; median mRS score at the onset of pregnancy: 1 [range, 1–2]). The main clinical features are shown in table 1 (further individual information in Supplemental Material, links.lww.com/NXI/A185). Median age was 23 years (range, 19–37 years), and all patients had combinations of symptoms typical for anti-NMDAR encephalitis, 7 of them (64%) requiring intensive care. An ovarian teratoma was found and removed in 4 (36%) patients. All patients survived, and at the last visit (median follow-up 28 months; range, 6–144 months), 8/11 (73%) had minor neurologic disability (mRS score ≤ 2). None of the 11 patients had obstetric complications, and all pregnancies were continued until delivery (table 2). A caesarean section was performed in 4 (36%) patients because of the severity of the neurologic disease, but there was no case of fetal distress. The postpartum period was uneventful in all cases.

Infants of the current series

In total, 11 children were born (5 females and 6 males), 6 (55%) preterm (table 3). Ten newborns (90%) were reported healthy after delivery, and the 5-minute APGAR score was

Table 1 Clinical features of the patients

	Present series	Literature
No. of cases	11	21
Median age (range)	23 (19–37)	25 (18–36)
NMDAR encephalitis during pregnancy, n (%)	6 (55)	21 (100)
Pregnancy onset during recovery phase, n (%)	5 (45)	0 (0)
Teratoma, n (%)	4 (36)	10 (48)
Clinical presentation		
First episode, n (%)	11 (100)	20 (95)
Relapse, n (%)	0 (0)	1 (5)
Symptoms, n (%)		
Psychotic symptoms	11 (100)	17 (81)
Anterograde amnesia	7 (64)	9 (43)
Seizures	6 (55)	13 (62)
Dyskinesia	7 (64)	14 (67)
Disintegration of speech	7 (64)	3 (14)
Impairment of consciousness	7 (64)	17 (81)
Central hypoventilation	3 (27)	9 (43)
Autonomic symptoms	5 (45)	9 (43)
Insomnia	2 (18)	3 (14)
Combination of ≥3 symptoms, n (%)	11 (100)	18 (86)
Psychotic and cognitive symptoms only, n (%)	0 (0)	2 (10)
Seizures only, n (%)	0 (0)	1 (5)
Admission in ICU, n (%)	7 (64)	18 (86)
Neurologic symptoms at the onset of pregnancy		
None, n (%)	6 (55)	21 (100)
Anterograde amnesia, n (%)	2 (18)	0 (0)
Depressed mood/anxiety, n (%)	2 (18)	0 (0)
Behavioral disturbances, n (%)	2 (18)	0 (0)
Reduced attention span, n (%)	1 (9)	0 (0)
Reduced speech fluency, n (%)	1 (9)	0 (0)
Immunotherapy during pregnancy		
Steroids, n (%)	4 (36)	17 (81)
IVIg, n (%)	4 (36)	11 (52)
Plasma exchange, n (%)	1 (9)	9 (43)
Rituximab, n (%)	1 (9)	3 (14)
Cyclophosphamide, n (%)	0 (0)	1 (5)
None, n (%)	4 (36)	3 (14)

Table 1 Clinical features of the patients (continued)

	Present series	Literature
Neurologic outcomes		
No. (%) with available follow-up	10 (91)	13 (68)
Median follow-up, mo (range)	28 (6–144)	9 (6–18)
Median mRS score at last follow-up (range)	1 (0–4)	1 (0–3)

Abbreviations: ICU = intensive care unit; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NMDAR = NMDA receptor.

normal in 6/6 (100%) (not provided for the other 5 newborns). One newborn, whose mother had developed NMDAR encephalitis at 20 weeks of gestation, presented with respiratory distress immediately after delivery (APGAR score not provided). This was considered an adverse effect of the antiepileptic and sedative drugs that had been administered to the mother, and the baby recovered spontaneously in less than 24 hours. Among 9 (81%) infants with follow-up (median 18 months; range, 7–96 months), no developmental abnormality, atypical behavior, or abnormal interaction was reported. Only 1 newborn was tested for serum NMDAR antibodies and was found positive; he was reported healthy at birth and at the last follow-up (18 months) showed normal development and behavior.

Review of previously reported patients

A review of the English literature identified 19 publications reporting 21 cases of anti-NMDAR encephalitis during pregnancy (table 1).^{2–8,13–24} Median maternal age was 25 years (range, 18–36 years), and 18 (85.7%) patients required intensive care. A teratoma was found and removed in 10/21 (47.6%) patients. Two patients (10%) died of septic shock during intensive care, one of them after the delivery of a baby (case with cortical dysplasia). Follow-up was provided for 13/19 (68.4%) survivors, and 12 (92.3%) of them had good neurologic outcomes (final mRS score ≤ 2). Obstetrical complications were reported in 7/19 (36.8%) patients (table 2). Two patients had miscarriages during the first trimester, and in another 2 patients, the pregnancy was terminated.^{2,17–19}

Review of outcomes of previously reported children

In total, 16 children were born, 9 (56%) preterm. A cesarean section was performed in 8 (50%) mothers, either because their clinical status was deteriorating (n = 5) or there was fetal distress (n = 3). Thirteen of 16 (81.3%) newborns were considered healthy. The APGAR score at 5 minutes was normal in 5/9 infants (56%; not provided for the other 7). One infant (mother's encephalitis at 7 weeks of gestation) had transient movement disorders after birth (5-minute APGAR score: 7/10) and during follow-up showed developmental delay and epilepsy due to cortical dysplasia.¹³ Another infant (mother's encephalitis at 37 weeks of gestation) was born

Table 2 Obstetrical outcomes in pregnancies concomitant with NMDA receptor encephalitis

	Present series	Literature
No. cases	6	21
Median age, range	23 (19–37)	24.5 (18–36)
Disease onset		
First trimester, n (%)	3 (50)	11 (52)
Second trimester, n (%)	2 (33)	7 (33)
Third trimester, n (%)	1 (17)	3 (14)
Complications		
Death from septic shock, n (%)	0 (0)	2 (10)
Obstetrical complications, n (%)	0 (0)	7 (33)
Spontaneous miscarriage	0 (0)	2 (10)
Uteroplacental insufficiency	0 (0)	1 (5)
Eclampsia	0 (0)	1 (5)
Hemorrhagic shock from vaginal bleeding	0 (0)	1 (5)
Unexplained fetal distress	0 (0)	2 (10)
Delivery		
No. (%) children born	6 (100)	16 (76)
Spontaneous miscarriage, n (%)	0 (0)	2 (10)
Death of the mother before delivery, n (%)	0 (0)	1 (5)
Medical termination of pregnancy, n (%)	0 (0)	2 (10)
Cesarean section, n (%)	4 (67)	8 (50)
Maternal indication^a	4 (100)	5 (63)
Fetal indication^b	0 (0)	3 (37)

^a Treatment or procedures used to treat the mother may affect the fetus.

^b The clinical status of the mother (e.g., severe autonomic dysfunction and uncontrolled seizures) is harmful to the fetus.

with hypotonia, hypoventilation, and seizure-like abnormal movements (5-minute APGAR score: 2/10).³ Brain MRI showed diffuse brain edema attributed to maternal antibody-mediated encephalitis, and he died 3 weeks after birth. Another infant (mother's encephalitis at 20 weeks of gestation) had transient neuromuscular symptoms and respiratory depression (APGAR score: 4/10) likely related to sedative drugs administered to the mother.⁸ Follow-up was available in 10 children (63%; median, 12 months; range, 6–36 months). All of them had normal development and behavior, except for the child with cortical dysplasia. Serum anti-NMDAR antibodies were tested in 6 newborns and found positive in 3, all with complications at birth (1 lethal encephalopathy; 1 cortical dysplasia with epilepsy and developmental delay, and 1 transient neuromuscular and respiratory deficit).

Immunotherapy during pregnancy

Immunotherapy was used in 7 (64%) patients studied by us and in 18 (86%) of the previously reported patients (table 1). No adverse effect was reported in any of the patients or infants. Twenty-one patients received IV steroids, 15 IV immunoglobulin (IVIg), and 10 plasma exchange. In addition, rituximab was administered to 4 patients (1 from our cohort and 3 from the literature). Rituximab was started during the first trimester (2 patients) or the second trimester (2 patients), at a median of 21 weeks (range, 19–33 weeks) before delivery. In all 4 patients, rituximab was well tolerated and associated with clinical improvement. One of these patients also received IV cyclophosphamide 6 weeks before delivery. In all 4 cases, the babies were healthy without malformations, hypogammaglobulinemia, or leukopenia. None of the patients studied by us or previously reported who had a low 5-minute APGAR score, or any symptoms at birth, were exposed to rituximab or cyclophosphamide during pregnancy.

Discussion

In this study, we aimed to assess the effects of anti-NMDAR encephalitis on pregnancy, focusing on the obstetrical complications and outcome of mothers and babies. Because it has been suggested that transplacental transfer of maternal NMDAR antibodies may be harmful to the fetus, we focused on 2 settings associated with maternal levels of serum NMDAR antibodies: (1) pregnant women who developed anti-NMDAR encephalitis and (2) women who became pregnant while they were recovering from anti-NMDAR encephalitis.²⁵ Placental transfer of maternal antibodies is critical for fetal protection against infections and begins at 12–13 weeks of pregnancy.^{26–28} However, at approximately the same time the blood-brain barrier of the fetus develops the ability to prevent the passage of endogenous albumin (and likely immunoglobulins) to the brain. Therefore, the amount of maternal antibodies that can actually reach the developing brain is unclear.^{29–31}

Despite in utero exposure to NMDAR antibodies (in some cases from the first trimester onward), up to 90% of infants studied by us were healthy at birth, and all of those who had assessable follow-up (7–96 months) had normal development. Premature birth was common due to the frequent indication of cesarean section, although without obvious adverse effects on the babies. Moreover, review of the literature shows that only 3 of 16 infants whose mothers had anti-NMDAR encephalitis during pregnancy developed neonatal encephalopathy.^{3,8,9} In 1 study, based in a single patient, the authors suggested that neonatal encephalopathy due to passive transfer of maternal NMDAR antibodies can potentially occur several years after the mother has recovered from the encephalitis as long as she remains anti-NMDAR seropositive.⁹ Other authors proposed that the absence of serum NMDAR antibodies in the mother (e.g., only detected in CSF) decreases the risk of problems in the newborn.⁵

Table 3 Children outcomes

	Present series	Literature
No. children	11	16
Term of delivery		
Full term, n (%)	4 (36)	3 (19)
Early term, n (%)	1 (9)	4 (25)
Preterm, n (%)	5 (45)	9 (56)
Extreme preterm, n (%)	1 (9)	0
Health status at birth		
Healthy, n (%)	10 (91)	13 (81)
Neuromuscular/respiratory depression, n (%)	1 (9)	1 (6)
Transient abnormal movements, n (%)	0 (0)	1 (6)
Severe encephalopathy and death, n (%)	0 (0)	1 (6)
APGAR score 5 min following delivery		
No. (%) with data	6 (54)	9 (56)
7–10, n (%)	6 (100)	5 (56)
4–6, n (%)	0 (0)	3 (33)
0–3, n (%)	0 (0)	1 (11)
Outcome at last visit		
No. (%) with available follow-up	9 (81)	10 (63)
Median follow-up, mo (range)	18 (7–96)	12 (6–36)
Healthy child with normal development, n (%)	9 (100)	7 (88)
Cortical dysplasia, epilepsy, and mental retardation, n (%)	0 (0)	1 (12)

Although all 3 reported infants with detectable NMDAR antibodies at birth had neurologic symptoms, in our series, the only newborn that tested positive was healthy. It is likely that the neurologic symptoms described in those infants resulted from a combination of factors that may include the potential pathogenic effects of the antibodies (usually transient) along with the side effects of sedatives, antiepileptics, and other drugs used during the pregnancy. Except for 1 previously reported baby with cortical dysplasia (along with delayed global development and seizures) who was the product of a pregnancy with multiple complications, uteroplacental insufficiency, and delivery at gestational age 34 weeks, we have not identified other infants with neurodevelopmental disorders.¹³

In addition to the infants' outcomes, we reviewed the importance of obstetrical complications in patients who develop anti-NMDAR encephalitis during pregnancy. Although in our series we did not identify obstetrical complications, about one third of reported patients had pathologic pregnancy or

spontaneous miscarriage that are likely related to the severe neurologic and medical problems of patients with this disease, often requiring intensive care admissions. Because pregnant patients with other diseases that may require prolonged intensive care are relatively infrequent in obstetrical cohorts, the comparison with those with anti-NMDAR encephalitis is difficult, and we have not been able to determine whether this disease causes more obstetric complications than other diseases that associate with similar degree of neurologic and systemic symptoms.^{32,33} Therefore, although the exact cause of these complications and their relation with anti-NMDAR encephalitis are unclear, autonomic dysfunction or seizures could have played a role. In late stages of pregnancy, uteroplacental blood flow comprises a large part of the maternal cardiac output, making the fetus particularly sensitive to variations of maternal blood pressure.³⁴ For example, 3 patients underwent emergency cesarean sections due to signs of fetal distress, resulting in good outcome in 2 of them.

In most pregnant patients, the immunotherapies used are those described as first-line treatments (steroids, IVIg, and plasma exchange). Our experience and that reported in the literature indicate that these treatments are usually well tolerated. The experience with rituximab (which is often considered a second-line treatment) is limited to a few patients, and it was well tolerated. Previous retrospective studies and literature reviews on pregnant patients with autoimmune demyelinating diseases treated with rituximab did not show adverse effects on patients or newborns.^{35,36} Low B-cell counts may be observed in the infants, but they usually normalize spontaneously in the first 6 months without increased infection rates.

This study has limitations posed by its retrospective nature and the small number of cases available. The short follow-up of the infants (median 18 months in our series and 12 months in the literature) and the lack of systematic neuropsychological assessment may have potentially missed neurologic complications. On the other hand, the current frequency of complications identified in the literature, despite being small, probably represents a reporting bias whereby cases with complications are more likely to be reported. Over the years, we have learned of additional cases (not included in this report, and unable to track) of pregnant patients with anti-NMDAR encephalitis who delivered healthy babies.

Despite these limitations, the current findings are important to report in light of a recent study by Jurek et al.,¹¹ suggesting that in asymptomatic pregnant women (without evidence of previous history of anti-NMDAR encephalitis), transplacental transfer of serum NMDAR antibodies results in neuropsychiatric symptoms in the offspring. This study is very disconcerting for patients and families of patients with anti-NMDAR encephalitis because during the disease, these patients have high levels of NMDAR antibodies that usually remain detectable (albeit at low titer) for many months or years after recovery. However, the conclusions

of Jurek et al.¹¹ are based in a model of passive transfer of high amounts (0.48 mg) of a monoclonal antibody derived from a patient with classic anti-NMDAR encephalitis to pregnant mice that resulted in 27% neonatal mortality and multiple symptoms during the postnatal and adult stages of the mice. This monoclonal antibody does not reflect the antibody repertoire of patients with anti-NMDAR encephalitis and, even less so, the antibodies of asymptomatic mothers of children with neurocognitive deficits. Moreover, there is no evidence that the antibodies of asymptomatic pregnant women (without a previous history of anti-NMDAR encephalitis) are the same as those antibodies occurring in anti-NMDAR encephalitis or have similar pathogenicity.

Overall, the current findings and previously reported cases suggest that in pregnant patients with anti-NMDAR encephalitis, fetal exposure to maternal NMDAR antibodies infrequently associates with overt neurologic deficits. Acute neonatal encephalopathy or neurodevelopmental disorders appear to be infrequent, and in such cases, other factors, not necessarily antibody related (e.g., drugs used during pregnancy, seizures or autonomic dysfunction of the mother, uteroplacental insufficiency, and premature delivery), may play a role. Obstetrical complications pose a serious threat to pregnant patients with NMDAR encephalitis, suggesting that these patients need to be monitored closely in intensive care units dedicated to high-risk pregnancies and treated early with first-line immunotherapy (e.g., steroids and IVIg). Considering our findings and those of larger series of patients with other CNS autoimmune disorders, rituximab is a potential treatment option in severely ill pregnant who fail first-line therapies.³⁵ Our results suggest that pregnancy is not contraindicated in women with a history of anti-NMDAR encephalitis. An important question to clarify is whether serum antibody titers in the mother and newborn correlate with the likelihood of neurologic deficits and developmental abnormalities. Future multi-institutional investigations on patients who develop anti-NMDAR encephalitis during pregnancy, or become pregnant after the acute phase of the disease, are needed. These studies should include neuropsychological assessments of the children with sufficient follow-up (24–36 months) to detect any delay in skill acquisition.

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