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CRITICAL REVIEW

Autoimmune encephalitis during pregnancy: A diagnostic and therapeutic challenge—A systematic review with individual patients' analysis and clinical recommendations

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Abstract

Several reports have described the autoimmune encephalitis' (AE) possible onset during pregnancy. In this systematic review, we summarize the available data on the diagnostic and therapeutic approach to AE during pregnancy, highlighting the associated maternal and fetal clinical outcomes. A systematic search of the literature was performed. The following databases were used: PubMed, Google Scholar, EMBASE, and CrossRef. The revision was registered on the PROSPERO platform (CRD42022336357). Forty-nine patients were included. AE onset was mainly observed during the first and the second trimester of pregnancy with psychiatric manifestations and seizures as main onset symptoms. CSF analysis

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showed AE-specific autoantibody positivity in 33 patients (anti-NMDA receptor as the most frequent). EEG generally showed normal findings. MRI revealed pathological findings in less than half of patients. Tumor screening was positive in 14 cases. First-line immunotherapy (single or combined) was generally employed while second line was administered in a minority of patients. Levetiracetam was the most used antiseizure medication. Cesarean section was performed in 18 women. Most of the women had an excellent early outcome after delivery but 22 showed persistent neurological deficits in long-term follow-up. Fetal outcome was positive in 33 cases, whereas 12 cases of fetal death were reported. A logistic regression showed that no variable significantly influenced the odds of good/bad maternal and fetal clinical outcome. Diagnosis and treatment of AE during pregnancy is challenging. The rate of miscarriage in women with AE seems to be higher than the general population. In addition, mothers may show long-term neurological deficits.

KEYWORDS

autoimmune encephalitis, diagnosis, pregnancy, teratogenic, therapy

1 | INTRODUCTION

Autoimmune encephalitis (AE) is a heterogeneous group of autoimmune-mediated disorders involving the central nervous system (CNS). Clinically, AE exhibit a variable association of cognitive and/or behavioral deficits, seizures, and movement disorders, sometimes preceded by a prodromal phase of flu-like symptoms.[1] In general, AE-specific autoantibodies target antigens that can be localized in different neuroglial components (i.e., oligodendrocytes, astrocytes, or neurons) and cellular compartments (i.e., the cell surface or intracellular space). However, up to 20% of patients with clinical suspicion of AE do not present identifiable antibodies in the serum or the cerebrospinal fluid (CSF). In this regard, a diagnosis of seronegative AE is made.[2]

Diagnosis of AE is made according to Grau s' criteria which are based on clinical (i.e., subacute onset of memory deficit or psychiatric symptoms), laboratory (i.e., cerebral spinal fluid pleocytosis), and instrumental (i.e., magnetic resonance imaging [MRI] scans of the brain) findings. In several cases, AE may be associated with underlying neoplasia, and this risk is also higher according to specific autoantibodies.[3] Breast, ovarian, testicular, and lung cancer (in particular, small-cell lung cancer) as well as Hodgkin's lymphoma, are the most frequent tumors associated with AE.[4]

Recent epidemiological studies indicate that AE have an estimated prevalence rate of 13.7/100000 and, while they can occur at any age, their prevalence is slightly higher in patients around 30 years, the median age being 43.[5] Several reports have emphasized possible AE onset during pregnancy.[6] Anti N-methyl-D-aspartate receptor (NMDAr) antibody encephalitis is one of the most frequently described forms of AE in pregnancy[7]; yet, other forms have also been reported. AE diagnosis and treatment during pregnancy are challenging due to the possible teratogenic effects of certain diagnostic procedures and therapeutic approaches. Especially in the first

Key points

- AE during pregnancy mostly occurs in the first and the second trimester with anti-NMDAR as the most common.
- Maternal short- and long-term clinical outcomes are most of the time favorable.
- The rate of miscarriage seems to be higher in pregnant women with AE than in the general population.
- First-line immunotherapy (i.e., corticosteroids, IgEV, or PLEX) is generally effective in AE treatment.
- Seizures are well controlled with a single antiseizure medication; levetiracetam is the most prescribed ASM.

trimester, the use of antiseizure medications (ASMs) such as valproate and phenobarbital,[8] immunomodulatory drugs (i.e., cyclophosphamide and rituximab),[9] or radiological examinations (e.g., computer tomography [CT] or magnetic resonance image [MRI] scans with contrast agents)[10] are associated with increased rates of intra-uterine death, congenital malformations (like spina bifida or cardiac anomalies), and newborn distress.

This systematic review aims to reassume and analyze the available data on the diagnostic and therapeutic approach to AE during pregnancy highlighting the associated maternal and fetal clinical outcomes.

2 | METHODS

2.1 | Searching strategy and reviewing organization

Results of this systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Ten authors (F.D., M.T., G.E., S.C., J.L., B.N., F.R., M.R., M.D.P., L.T., S.T., D.C., M.D.A., V.P., and F.N.) independently searched from the first available date up to August 2022. The search terms were combinations of the following: "autoimmune encephalitis," "pregnancy," "maternal outcome," "obstetric delivery," "'pregnancy complication," "abortion," and "fetal outcome." The full search strategy is outlined in the Table S1. The following electronic databases and data sources were systematically searched: MEDLINE (accessed through PubMed), EMBASE, and Google Scholar.

The quality of the studies included in the quantitative analysis was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS).[11] This score ranges from 0 to 9, with studies scoring above 5 evaluated as good quality. Ten reviewers (F.D., M.T., G.E., S.C., J.L., B.N., F.R., M.R., M.D.P., L.T., S.T., D.C., M.D.A., V.P., and F.N.) independently screened the retrieved articles for possible inclusion. Disagreements were collegially discussed and resolved through discussion. Data were extracted on a digital spreadsheet.

We extracted and collected the following individual patient data: age, comorbidity (Yes or No), previous epilepsy diagnosis (Yes or No), gestational age, diagnosis of AE and specific type of auto-antibody, serum and/or cerebrospinal fluid (CSF) antibody positivity, first symptom of AE (e.g., seizure, psychiatric manifestations, cognitive impairment, cephalalgia, and other neurological symptoms), neuroradiological assessment (MRI or CT both with or without contrast), electroencephalogram (EEG), malignancy (Yes or No), radiological approach to malignancy diagnosis (i.e., radiation-based vs non radiation-based techniques both with or without contrast), AE immunological treatment (i.e., oral or intravenous steroids, immunoglobulins, plasma exchange, azathioprine, cyclophosphamide, mycophenolate, and rituximab), ASM treatment, malignancy surgery (Yes or No), antipsychotic treatment, fetal outcome (i.e., safe at term, preterm, and abortion), maternal short-term outcome (i.e., complete responder, poor responder, and death), and long-term maternal outcome. The entire list of variables used for statistical analysis and missing data are reported in Table S2.

The final study protocol was registered in the PROSPERO international prospective register of systematic review (https://www.crd.york.ac.uk/PROSPERO/, registration number CRD42022336357).

2.2 | Statistics

Statistical analysis was performed on the final dataset containing all information pooled from the studies selected by our systematic review. Data were analyzed in Statistical Package for Social Science (SPSS®) software version 22 (SPSS, Inc.). The normality of continuous data was checked via the Kolmogorov–Smirnov test, and a logistic (Forward Stepwise) regression was used to describe how clinical variables modified the odds of maternal and fetal outcome. We used a chi-squared test to compare the distribution of clinical features between patients who survived and those who did not. The alpha level was set at 0.05 for statistical significance.

3 | RESULTS

3.1 | Literature search

The literature search reported above yielded 4306 articles (MEDLINE: 336 results; Google Scholar: 3070; EMBASE: 880; and other sources: 20). Of the 4306 records screened, the full texts of 62 articles were reviewed for eligibility. Twenty-two articles initially considered for possible inclusion were eventually excluded (excluded articles with reasons for exclusion are reported in Table S3). Forty studies (36 case reports and four case series) fulfilling the selection criteria were finally included (Figure 1). According to Newcastle–Ottawa Quality Assessment Scale (NOS), 16 articles received a score of 5, 19 articles had a score of 4, and 5 articles were scored 3 (score results in detail are shown in Table S4). Details of the included articles are reported in Table 1.[7,12–51]

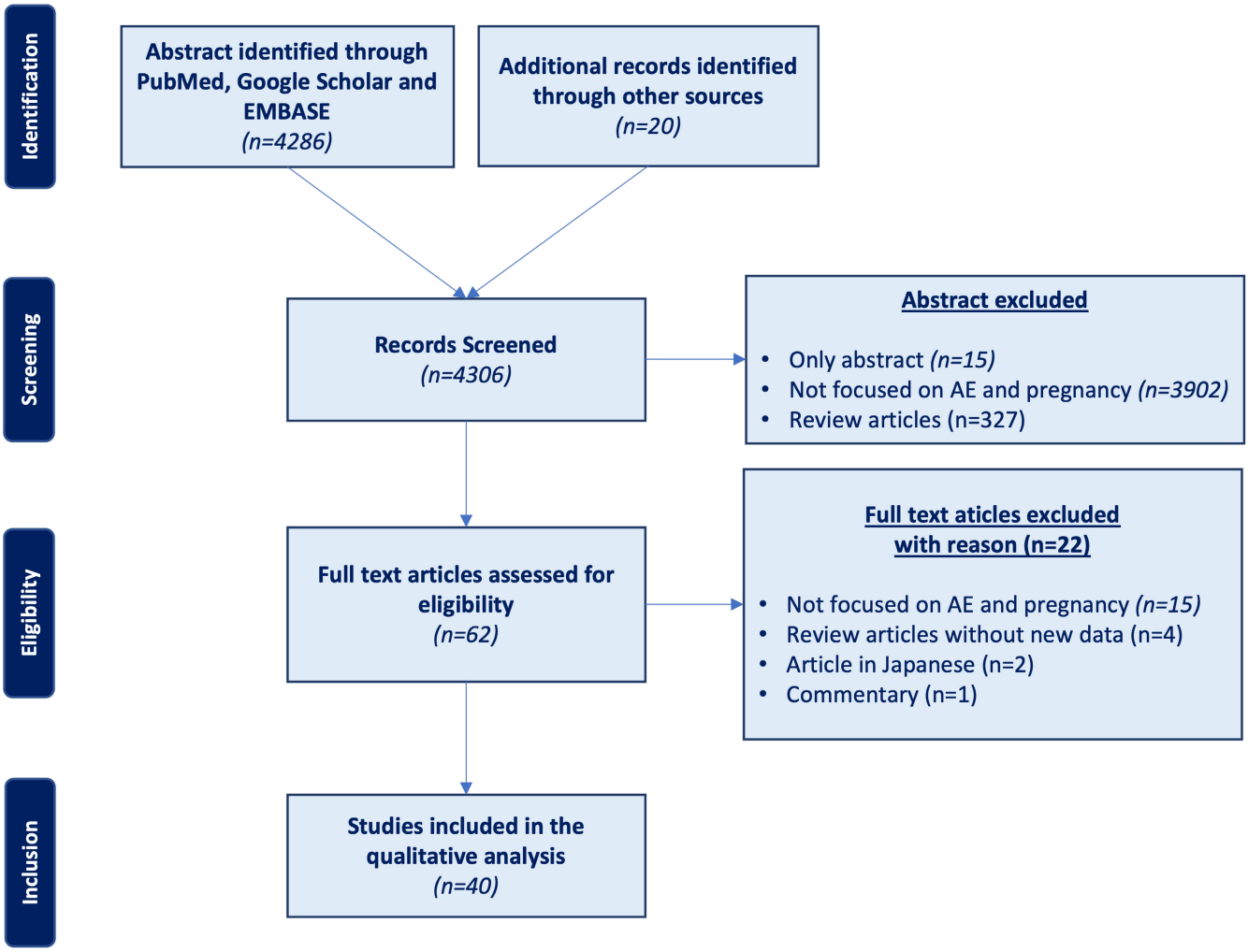

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram describing the search from literature; 4306 records were screened from which 40 articles were selected. AE, autoimmune encephalitis.

3.2 | Clinical features

Data from 49 patients with an average age of 26.3 ± 5.6 years (range: 19–37) were extrapolated from the included studies. The gestational age at AE onset was within the first trimester weeks in 21 patients (21/49, 42.9%), in the second trimester in 20 patients (20/49, 40.8.%), whereas in the third in 8 patients (8/49, 16.3%).

Diagnosis of AE was made according to Graus criteria in all cases. No patients presented prodromal flu-like symptoms before AE onset. As first clinical presenting symptom, 33 patients (33/49, 67.3%) exhibited psychiatric manifestations, in particular visual hallucinations and acute psychosis; 20 patients (20/49, 40.8%) showed focal or focal-to-bilateral tonic–clonic seizures; 16 patients showed headache (16/49, 32.7%), 10 patients (10/49, 20.4%) showed cognitive impairment, whereas 19 (19/49, 38.8%) had other neurological symptoms among which the most frequent were movements disorders, abnormal facial movements, impaired speech, drowsiness, pyramidal signs, postural instability, central hypoventilation, neurological urinary retention, impaired eye movements, and bulbar palsy. In this context, 21 patients (21/49, 42.8%) presented an overlap of two presenting symptoms (i.e., eight seizures plus psychiatric manifestations, four seizures plus headache, three seizures plus other neurological symptoms, two psychiatric manifestations and headache, two psychiatric menifestations and other neurological symptoms, one cognitive impairment and psychiatric manifestations, and one cognitive and other neurological symptoms) while 16 patients (16/49, 32.6%) presented an overlap of three or more presenting symptoms (i.e., four seizures plus psychiatric manifestations plus other neurological symptoms, three seizures plus psychiatric manifestations plus headache, two psychiatric manifestations plus headache plus other neurological symptoms, two psychiatric manifestations plus cognitive impairment plus other neurological manifestations, one headache plus cognitive impairment plus other neurological symptoms, one seizures plus psychiatric manifestations plus cognitive impairment, one

seizures plus psychiatric manifestations plus headache plus cognitive impairment, one seizures plus psychiatric menifestations plus cognitive impairment plus other neurological manifestations, and one seizures plus psychiatric menifestations plus headache plus cognitive impairment plus other neurological symptoms).

During the disease, 34 patients (34/49, 69.4%) eventually suffered from new onset seizures with 14 patients (14/49, 28.6%) reporting the occurrence of status epilepticus. Of note, as previously shown, among these 34 patients 20 individuals showed seizures as AE presenting symptom. Due to the severity of symptoms, 25 patients (25/49, 51%) were admitted to the Intensive Care Unit (ICU).

Data on AE's first clinical symptoms are reported in Figure 2.

3.3 | Diagnostic workup

The results of the CSF analysis were reported in 44 cases (44/49, 89.8%) and showed cellular pleocytosis in 30 patients (30/49, 61.2%) and AE-specific autoantibody positivity in 33 cases (33/49, 67.3%). CFS oligoclonal band positivity was reported in just four cases (4/49, 8.2%). Serum autoantibodies were detected in 31 cases (31/49, 63.3%), of which only 21 were also confirmed in the CSF. Twelve patients (12/49, 24.5%) tested negative in the serum, resulted positive for autoantibodies in the CSF. The most frequent autoantibodies detected were against the anti-NMDAr in 37 patients (37/49, 75.5%), whereas anti-TPO and anti-GAD 65 positivity was reported in three (3/49, 6.1%) and two (2/49, 4.1%) patients, respectively. Two patients (2/49, 4.1%) had multiple autoantibodies positivity (i.e., anti-NMDA, anti-GAD 65, and anti-TPO in both patients). A diagnosis of seronegative AE was made in six patients (6/49, 12.2%), according to the high clinical suspicious (e.g., subacute onset of psychiatric symptoms associated with seizures) supported by laboratory (e.g., CSF pleocytosis or increased proteins level) and neuroimaging findings (e.g., brain MRI hypersignal over mesial temporal regions). The full list of the specific autoantibodies' positivity is reported in Table 2.

Electroencephalogram (EEG) analysis was performed in all patients, with 21 indicating normal findings (21/49, 42.9%). Diffuse theta/delta slowing was reported as the main pathological finding, whereas epileptiform discharges were detected in only seven cases (7/49, 14.3%). Extreme delta brush (EDB) pattern was reported in two cases both associated with NMDA-R autoantibodies positivity.

MRI scans of the brain findings were reported in 31 patients (31/49, 63.3%). In all cases, MRI was performed without contrast. As a result, 14 cases (14/49, 28.6%) presented a normal MRI, whereas 13 patients (13/49, 26.5%) presented hyperintense signal changes on T2-weighted and T2-FLAIR sequences, mostly in the temporal region. Nonspecific abnormal MRI findings were reported in four patients (4/49, 8.2%).

The search for underlying neoplasia was reported in 44 cases (44/49, 88.5%). A tumor was found in 14 patients (14/49, 28.6%) with ovarian teratoma in 13 patients (13/49, 26.5%), and an ovarian lesion not otherwise specified in one patient (1/49, 2%). All patients with an underlying tumor were tested positive for anti-NMDAr antibody.

Extensive information about patients' diagnostic workups is reported in Table 2.

3.4 | Treatment of AE and related symptoms

3.4.1 | Immunomodulant treatment

A total of 44 patients (44/49, 89.8%) received immunomodulant treatment (IMT). Thirty (30/49, 61.2%) patients were treated with single or combination first-line IMT (i.e., corticosteroids, intravenous immunoglobulins [IVIg], or plasma exchange [PLEX]). Of those patients treated with single first-line IMT, five women (5/49, 10.2%) received only intravenous corticosteroid treatment, 3 (3/49, 6.1%) plasmapheresis (PLEX), while none was treated with IVIg alone. Notably, 36 patients (36/49, 73.5%) underwent a combined first-line therapy (i.e., corticosteroids + IVIg, corticosteroids + PLEX, IVIg + PLEX, or all three first-line IMT).

Second-line immunosuppressive treatments were administered in a minority of patients (14/49, 28.6%). Specifically, the use of rituximab (RTX), cyclophosphamide (CYC), and azathioprine (AZA) was reported in ten (10/49, 20.4%), five (5/49, 10.2%), and three (3/49, 6.1%) patients, respectively. Four patients (4/49, 8.2%) received combined second-line therapy (i.e., CYC and RTX). No patients were treated with mycophenolate mofetil (MFM).

Thirteen patients (13/49, 26.5%) underwent abdominal surgery (i.e., oophorectomy) to remove the underlying tumor.

3.4.2 | Antiseizure treatment

Specific antiseizure treatment was reported in 30 cases (30/49 61.2%), with a median of 1 (IQR 0–2) ASM. Levetiracetam (LEV) was the most widely used ASM (18/49, 36.7%), followed by lamotrigine (LMT) in five patients

TABLE 1 Details of included articles.

Study	Total no of cases	Autoantibodies	Age	Gestational week	Steroid treatment
Yi-Chia Wei et al., 2013	1	AMPA	30	11	Oral prednisolone and i.v. Dexamethasone
I. Funakawa et al., 1999	1	Anti Gq1b	23	13	
R, A. J. Larner et al., 1995	1	Seronegative	22	3	
Hiroaki Yaguchi et al., 2012	1	AQP4	NS	8	Oral prednisolone and nonspecified i.v. corticosteroid
S. Zhang et al., 2020	1	Anti-NMDA	23	12	Oral prednisolone
H. Liu et al., 2021	2	1) Anti NMDAr	19	8	Oral and i.v. methylprednisolone
		2) Anti-NMDAr	21	10	
B. Joubert et al., 2020	6	1) Anti-NMDAr	1	25	Oral and i.v. methylprednisolone
		2) Anti-NMDAr	37	33	
		3) Anti-NMDAr	31	20	
		4) Anti-NMDAr	25	5	
		5) Anti-NMDAr	20	12	
		6) Anti-NMDAr	23	8	
P. Jagota et al., 2014	1	Anti-NMDA	18	9	
C. McGuigan et al., 2012	1	VGKC	26	32	
N. Maher et al., 2011	1	Seronegative	34	NA	
D. Prawesti et al., 2018	1	Anti-NMDA	34	NA	Oral and i.v. methylprednisolone
L. Shahani, 2015	1	Anti-NMDA	26	22	I.v. methylprednisolone
L.W. Chan et al., 2015	1	Anti-NMDA	23	First trimester	–
L.M. Lamale-Smith et al., 2015	1	Anti-NMDA	24	20	–
K.O. Jung et al., 2020	1	Anti-NMDA	28	24	–
N. Kokubun et al., 2016	1	Anti-NMDA	25	9	–
A. Colpo et al., 2019	1	Seronegative	29	17	–

Immunoglobulin (IgEV) and/or plasmapheresis (PLEX)	Second-line immunosuppressive treatment	Maternal outcome	Newborn outcome
PLEX	Azathioprine	Alive but persistent long-term moderate–severe deficit	Fetal death
PLEX	–	Alive without neurological deficit	–
–	–	Alive but persistent long-term moderate–severe cognitive and motor deficit	–
IgEV	–	Alive but persistent long-term moderate–severe cognitive and motor deficit	Born healthy
IgEV	–	Alive without neurological deficit	Fetal death
1) IgEV	–	1) Alive but persistent mild long-term cognitive deficit	1) Fetal death
2) IgEV	–	2) Alive but persistent mild long-term cognitive deficit	2) Fetal death
1) IgEV PLEX	1) Rituximab Ciclophosphamide	1) Alive but persistent long-term moderate–severe cognitive and motor deficit	1) Born healthy
2) IgEV	2) Ciclophosphamide	2) Alive without neurological deficit	2) Born healthy
3) IgEV	3) Rituximab Ciclophosphamide	3) Alive but persistent long-term mild cognitive and motor deficit	3) Born healthy
4) IgEV PLEX	4) Rituximab	4) Alive with cognitive deficit and need help for activities of daily living	4) Preterm birth
5) IgEV	5) –	5) Alive but persistent mild long-term cognitive deficit	5) Born healthy
6) IgEV	6) –	6) Alive but persistent mild long-term cognitive deficit	6) Born healthy
IgEV	–	Dead due to superimposed infection	Preterm born with cognitive impairment
–	–	Alive but persistent long-term moderate–severe cognitive and motor deficit	Born healthy
–	–	–	–
IgEV PLEX	–	Alive without neurological deficit	Born healthy
PLEX	–	Alive without neurological deficit	Born healthy
PLEX	Rituximab	Alive but persistent mild long-term cognitive deficit	Fetal death
IgEV PLEX	Rituximab	Alive but persistent mild long-term cognitive deficit	Preterm birth
IgEV	Rituximab	Alive but persistent mild long-term cognitive deficit	Born healthy
–	–	Alive without neurological deficit	Fetal death
PLEX	–	Alive but persistent mild long-term cognitive deficit	Born healthy

TABLE 1 (Continued)

Study	Total no of cases	Autoantibodies	Age	Gestational week	Steroid treatment
S. Stamenova et al., 2021	1	Anti-MOG	31	31	–
E. Mizutamari et al., 2016	1	Anti-NMDA	30	15	I.v. Methylprednisolone
X. Xiao et al., 2017	1	Anti-NMDA	24	28	–
S. Kalam et al., 2019	1	Anti-NMDA	34	8	–
L. Demma et al., 2017	1	Anti-NMDA	28	16	–
M. Tailland et al., 2020	1	Anti-NMDA	37	18	–
Y.T. Lu et al., 2017	2	1) Seronegative	21	26	1) I.v. Methylprednisolone
		2) Seronegative	23	5	–
K.S. Grewel et al., 2018	1	Anti-NMDA	25	16	–
S.R. Sharma et al., 2014	1	Anti-TPO	21	24	–
M.M. Sperling et al., 2021	1	Anti-NMDA	33	14	–
S. Mathis et al., 2015	1	Anti-NMDA	21	10	–
M.A. Kumar et al., 2010	3	1) Anti-NMDA	19	14	–
		2) Anti-NMDA	20	8	–
		3) Anti-NMDA	19	17	–
Jesslyn Lu et al., 2015	1	Anti-NMDA, anti-GAD 65, anti-TPO	36	6	–
K. Nishiyama et al., 2007	1	Seronegative	34	20	–
N. Chourasia et al., 2017	1	Anti-NMDA	32	37	–
A. Ueda et al., 2017	1	Anti-NMDA	22	22	I.v. methylprednisolone
J. Kim et al., 2015	1	Anti-NMDA	28	7	–
A.O. Keskin et al., 2019	1	Anti-NMDA	27	18	–
M. Goyal et al., 2014	1	Anti-TPO, anti-NMDA, anti-GAD	36	4	–
Y. Ito et al., 2010	1	Anti-NMDA	19	17	–

Immunoglobulin (IgEV) and/or plasmapheresis (PLEX)	Second-line immunosuppressive treatment	Maternal outcome	Newborn outcome
–	Azathioprine	Alive but persistent mild long-term cognitive deficit	Born healthy
IgEV PLEX	–	Alive without neurological deficit	Born healthy
IgEV	–	Alive without neurological deficit	Preterm birth with low weight
IgEV PLEX	–	Alive without neurological deficit	Born healthy
IgEV PLEX	Rituximab and Ciclophosphamide	Alive but persistent mild short-term cognitive deficit	Born healthy
IgEV	–	Alive but persistent long-term moderate–severe cognitive and motor deficit	Born healthy
1) – 2) PLEX	1) – 2) –	1) Alive but persistent mild long-term cognitive deficit 2) Dead	1) Preterm birth with respiratory complications 2) Fetal death
IgEV	Rituximab	Alive without neurological deficit	Born healthy
IgEV	–	Alive without neurological deficit	Fetal death
IgEV PLEX	–	Alive but persistent mild long-term cognitive deficit	Born healthy
IgEV	–	Alive but persistent mild long-term cognitive deficit	Born healthy
1) IgEV PLEX	–	1) Alive but persistent long-term moderate–severe cognitive and motor deficit	1) Born healthy
2) IgEV	–	2) Alive without neurological deficit	2) Fetal death
3) –	–	3) Alive without neurological deficit	3) Born healthy
PLEX	–	Alive without neurological deficit	Born healthy
–	–	Alive without neurological deficit	Born healthy
–	–	–	Born with respiratory distress and died at day 20
IgEV PLEX	–	Alive without neurological deficit	–
IgEV PLEX	Rituximab	Alive without neurological deficit	Fetal death
PLEX	–	Dead	Fetal death
PLEX	–	Alive without neurological deficit	–
–	–	Alive without neurological deficit	Preterm birth

TABLE 1 (Continued)

Study	Total no of cases	Autoantibodies	Age	Gestational week	Steroid treatment
F. Dono et al., 2022	1	Anti-NMDA	29	7	–
A. McCarthy et al., 2012	1	Anti-NMDA	32	8	I.v. methylprednisolone
Z. Liao et al., 2017	1	Anti-NMDA	24	29	–

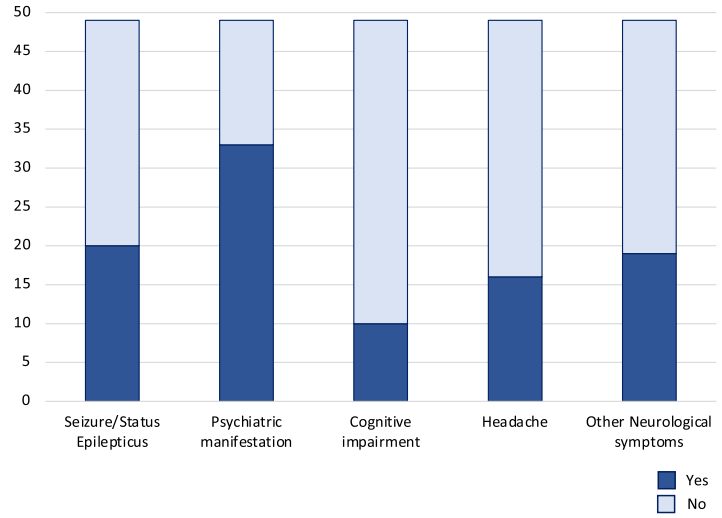

FIGURE 2 First symptoms associated with autoimmune encephalitis onset during pregnancy. Other neurological symptoms include movement disorders, abnormal facial movements, impaired speech, drowsiness, pyramidal signs, postural instability, central hypoventilation, neurological urinary retention, impaired eye movements, and bulbar palsy. SE, status epilepticus.

(5/49, 10.2%). Sodium channel blockers drugs were introduced in 16 (16/49, 32.7%) cases, namely Lamotrigine (LMT, five cases), Lacosamide (LCS, four cases), Phenytoin (PHT, six cases), and Carbamazepine (CBZ, three cases).

Treatment of status epilepticus was reported in 14 (14/49, 28.6%) patients. In all patients, the first-line treatment consisted of the administration of benzodiazepines (BDZ) in combination with a further ASM. In particular, the most used ASMs were LEV (7/14, 50%), followed by PHT (6/14, 42.9%) and VPA (3/14, 21.4%). More than half of the cases (8/14, 57.1%) responded to the first-line treatment. However, six patients (6/14, 42.9%) developed a refractory status epilepticus, and infusion therapy with anesthetic drugs was necessary. Three patients (3/6, 50%) were treated with continuous infusion of midazolam, whereas the other three (3/6, 50%) were treated with propofol infusion.

Extensive information about patients' treatment is reported in Table 3.

3.4.3 | Antipsychotics and other treatments

Antipsychotic treatment (APT) was reported in six cases (6/49, 12.2%). Haloperidol was the most frequently employed APT, followed by olanzapine, quetiapine, and tiapride.

3.5 | Maternal short and long-term outcomes

The type of delivery was reported in 23 (23/49, 46.1%) cases with cesarean section performed in 18 (18/49, 36.7%) and vaginal delivery in five cases (5/49, 9.6%).

Most of the women had an excellent short-term outcome after delivery, including those patients with multiple autoantibodies positivity. However, three women (3/49, 6.1%) in their first pregnancy trimester (two with anti-NMDAr antibodies and one with seronegative AE) died during the acute phase of the AE. In this context,

Immunoglobulin (IgEV) and/or plasmapheresis (PLEX)	Second-line immunosuppressive treatment	Maternal outcome	Newborn outcome
PLEX	–	Alive without neurological deficit	Born healthy
PLEX	Azathioprine	Alive without neurological deficit	Born healthy
IgEV PLEX	Rituximab and Ciclophosphamide	Alive without neurological deficit	Preterm birth

all the patients reported severe manifestations associated with AE (i.e., refractory status epilepticus in two cases and pneumonia in one case).

Of the 43 patients in long-term follow-up (median: 180 days, IQR: 41–5-540 days), 22 (22/43, 51.2%) reported a return to complete well-being. On the other hand, 21 women (21/43, 48.8%) showed persistent deficits. Mild to moderate cognitive impairment was reported in 15 patients, and five patients manifested moderate–severe motor deficits (hemiparesis and motor slowing), which improved after a rehabilitation program. Persistence of psychiatric symptoms, mainly depression and anxiety, was reported in a minority of patients. In all cases, these symptoms disappeared within 12 months.

Epilepsy was well controlled in all patients, except for two (2/43, 4.7%), one seronegative and one with anti-NMDAr antibodies, who reported persistence of critical episodes at follow-up, albeit markedly reduced.

Of the 14 patients who developed SE, a good short-term outcome was found in four cases (4/14, 28.6%). In eight patients (8/14, 57.1%), persistent deficits were reported at discharge, particularly moderate cognitive and motor deficits, and two patients (2/14, 14.3%) who developed SE eventually died.

A logistic regression was performed to evidence predictors of maternal outcome in the pooled population. No variable significantly influenced the odds of good/bad maternal clinical outcomes. Furthermore, there was no significant difference in the distribution of clinical variables between the good/bad outcome population.

Extensive information about maternal short and long-term outcome are reported in Table 4.

3.6 | Fetal short and long-term outcomes

Data regarding short-term fetal outcomes were reported in 45 cases. In thirty-three women (33/45, 73.3%), the pregnancy was unremarkable and led to normal delivery, although premature births were reported in seven cases and were associated with low birth weight. At birth, most infants have been described as neurologically and developmentally normal, with a median 5-min APGAR score of 6 (IQR: 6–9). Only in four cases (4/45, 8.9%), admission to the Neonatal Intensive Care Unit was required. Even at the follow-up visit, most cases showed no significant sequela for the newborns. However, 12 cases (12/45, 26.7%) of fetal death were reported. Notably, there were 11 cases of miscarriage, while one infant was born prematurely and died shortly after due to severe neonatal complications. Of the 11 miscarriages, nine (75%) were associated with AE onset during the first trimester. Of the 12 fetal deaths, nine (75%) were associated with NMDAr antibodies, one patient (8.3%) with anti-TPO antibodies, and one (8.3%) with anti-AMPA antibodies, whereas in one case (8.3%), the specific autoantibody was unknown.

In two cases, fetal death was associated with or followed by mother deaths. In the latter, one case was associated with anti-NMDAr antibody positivity, while the other was diagnosed as seronegative AE.

A logistic regression was performed to evidence predictors of fetal outcome in the pooled population. No variable significantly influenced the odds of good/bad fetal clinical outcomes.

Extensive information about fetal short and long-term outcome are reported in Table 4.

4 | DISCUSSION

Our analysis shows that AE onset can be observed during the entire pregnancy, although a higher incidence was found in the first and second trimester. While publication bias should be considered, we stress that anti-NMDAR encephalitis is the most common form of AE described during pregnancy. From a pathophysiological point of view, it must be pointed out that only one out of four patients showed associated neoplasia as a probable underlying cause of AE onset. Thus, pregnancy-related changes in the autoimmune system might play a pivotal role. Pregnancy is generally considered an anti-inflammatory state associated with decreased lymphocyte T proliferation and

TABLE 2 Patients' diagnostic workup.

	Total patients (n = 49)
Cerebrospinal fluid (CSF) analysis	
Normal cells	14 (28.6%)
Pleocytosis	30 (61.2%)
Lymphocytic	20
Monocytic	2
Other	1
Not known	7
CSF proteins >45 mg/dL	12 (24.5%)
CSF glucose >80 mg/dL	1 (2%)
Other findings	
Oligoclonal Bands	4 (8.2%)
Antibody positivity	
Total	43 (87.8%)
Serum	31 (63.3%)
CSF	33 (67.3%)
Both	21 (42.9%)
Number of antibodies detected	
Seronegative	6
One	41
Three	2
Types of antibodies	
anti-NMDAr	37
anti-TPO	3
anti-GAD65	2
anti-AMPAr	1
anti-Gq1b	1
anti-MOG	1
anti-VGKC	1
anti-AQP4	1
MRI findings	
Normal	14 (28.5%)
Atypical	17 (34.7%)
T2/FLAIR hyperintensity	13
Other findings	4
Not performed/Not indicated	18 (36.7%)
EEG findings	
Normal	21 (42.9%)
Atypical findings	28 (57.1%)
Diffuse slowing (theta or delta waves)	28
Epileptiform discharges	7
Extreme delta brush	2
Screening for malignancies	
Yes	44 (89.8%)
Pelvic MRI	9
Pelvic CT	4
Abdominal ultrasound	3
Not specified	28
NA	5 (10.2%)
Positive findings	14 (28.6%)
Ovarian teratoma	13
Ovarian lesion not otherwise specified	1

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AQP4, aquaporin 4; CT, computerized tomography; GAD65, glutamic acid decarboxylase 65; Gq1b, ganglioside Gq1b; MOG, Myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NA, not applicable; NMDAr, N-methyl-D-aspartate receptor; TPO, Thyroid peroxidase; VGKC, voltage-gated potassium channel.

loss of B and T cells responsiveness to mitogenic stimulation.[52] In this regard, it has been demonstrated that the hormonal modifications observed during pregnancy (i.e., the increase of estradiol and progesterone) may promote the differentiation of T lymphocytes in the Th2 state and lower the absolute number of plasmablasts, thus reducing the production of immunoglobulins.[13] These changes are more evident during the late stage of pregnancy and may support the higher incidence of AE during the first trimester. However, a Th2 state may increase the risk of AE onset. Th2-cell recruitment has been largely studied, especially in anti-NMDAR encephalitis. In this context, an increased level of C-C motif chemokine ligand (CCL)-22 (a Th2-derived chemokine) has been described in 70 patients suffering from anti-NMDAR encephalitis. CCL22 levels correlated with the severity of the clinical features.[53] CCL22 produces the recruitment of Th17 cells, increasing the Th17/Treg ratio, a hallmark of autoimmunity as described in other autoimmune diseases like psoriasis, rheumatoid arthritis, and multiple sclerosis. Thus, Th17 and Th2 may synergically mediate the cellular response in anti-NMDAR encephalitis.

From a diagnostic point of view, our results highlight that during pregnancy, brain MRI findings may be normal in most of cases of AE. In addition, EEG and CSF analysis may show normal or close-to-normal findings even within the acute phase of the disease. However, the serum and/or CSF detection of AE-specific antibodies generally guided the diagnosis. Surprisingly, antibodies detection was not always consistent between serum and CSF as demonstrated in 10 cases (i.e., one patient with anti-AMPA antibodies, six patients with anti-NMDA antibodies, one patient with anti-VGKC antibodies, one patient with anti-MOG antibodies, and one patient with anti-TPO antibodies). This intriguing finding could be related to the possible low sensitivity of the laboratory tests employed

TABLE 3 Patients' treatment regimen.

	Total patients (n = 49)
Hospitalization setting	
Available information	
No need of ICU admission	24 (49%)
Admission in ICU	25 (51%)
Immunomodulant treatment	
Median IMT number (IQR)	1 (0–2)
Corticosteroids	40 (81.6%)
Intravenous steroids only	24
Intravenous and oral steroids	16
Intravenous immunoglobulins	28 (57.1%)
Plasmapheresis	23 (46.9%)
Other immunosuppressive therapy	
Rituximab (RTX)	10 (20.4%)
Cyclophosphamide (CYC)	5 (10.2%)
Azathioprine (AZA)	3 (6.1%)
No immunosuppressive therapy	5 (10.2%)
Surgical procedure	
Yes	13 (26.5%)
No	36 (73.5%)
Antiseizure treatment	
Treated patients	30 (61.2%)
Median ASM number (IQR)	1 (0–2)
Levetiracetam	18
Na^+ blockers	16
Lamotrigine	5
Lacosamide	4
Phenytoin	6
Carbamazepine	3
Valproic acid	6
Vigabatrin	1
Gabapentin	1
Benzodiazepines	
Lorazepam	2
Clonazepam	2
Clobazam	4
Unknown	4
No treatment	18
Antipsychotic treatment	
Treated patients	6 (12.2%)
Median drug number (IQR)	0 (0–1)
Haloperidol	4
Olanzapine	3
Quetiapine	1
Tiapride	1

Abbreviation: ICU, intensive care unit.

TABLE 4 Maternal and fetal short and long-term outcome.

	Total patients (n = 49)
Age ± SD	26.35 ± 5.6
Gestational age	
Available information	
First trimester	21 (42.9%)
Second trimester	20 (40.8%)
Third trimester	8 (16.3%)
Delivery	
Available information	23 (46.9%)
Cesarean section	18 (36.7%)
Vaginal delivery	5 (10.2%)
Maternal short-term outcome	
Available information	
Complete well-being	20 (40.8%)
Death	3 (6.1%)
Persistent deficits	22 (44.9%)
Mild moderate cognitive impairment	15 (30.6%)
Moderate to severe motor deficits	7 (14.3%)
Maternal long-term outcome	
Available information	43
Complete well-being	22 (51.2%)
Mild to moderate cognitive impairment	15 (34.9%)
Moderate to severe motor and cognitive deficits	5 (11.6%)
Speech disorder	2 (4.6%)
Persistent seizures	2 (4.6%)
Newborn short-term outcome	
Available information	45
Born healthy	33 (73.3%)
Preterm birth	7 (15.6%)
Fetal death	12 (26.7%)
Abortion	11 (24.4%)
Died shortly after born	1 (2%)
Unknown	4 (8.9%)
APGAR score	6 (IQR: 6–9)
Newborn long-term outcome	
Available information	33
Normal development	20 (60.6%)
Mild developmental problems	5 (15.1%)
Development problems and seizures	1 (3%)
Not indicated	7 (21.2%)

in antibody search, though specific method in antibody searching (e.g., cell-based assay, CBA, or immunofluorescence essay, IFA) was available just in eight cases (six IFA and two CBA).

The sole presence of serum AE-specific autoantibodies generally causes some doubts in the diagnosis and treatment of AE since their neuropathogenic role is controversial. Nevertheless, recent experimental data stress that serum AE antibodies may modulate brain functions especially when there is a concomitant compromised brain–blood barrier (BBB) functioning.[54] Indeed, according to the "brain immunoprecipitator" theory,[55] the BBB leakage may promote AE-specific serum antibodies transfer to CNS where they rapidly bind all the specific brain antigens, thereby preventing their detectability into the CSF. On the other hand, the consequent antibodies' CSF expression is believed to be derived from an additional intrathecal synthesis which causes the antibodies spillover into the CSF. In line with this theory, BBB integrity testing (through MRI brain scan or CSF analysis) is encouraged to ascertain the pathological significance of a given serum AE antibody. Interestingly, in all aforementioned patients presenting serum/CSF discrepancy, CSF findings supporting a leakiness of the BBB (i.e., increased proteins and albumin levels) were reported, confirming the potential neuropathological role of serum antibodies.

Although clinical manifestations largely depend on specific AE types, we believe that new-onset seizures and psychiatric manifestations during pregnancy should raise suspicion of AE. Indeed, these symptoms were mostly reported regardless of the specific autoantibodies detected. Above all, a higher incidence of psychiatric manifestations has been reported in the first and second trimester of pregnancy. However, our data does not allow us to infer any strong phenotype specificity of AE according to the semester of onset due to the possible reporting bias.

The therapeutic approach of AE should consider two goals: Treatment of the inflammation with immunomodulatory therapy (IMT) and treatment of the accompanying neurological manifestations (especially seizures and psychiatric symptoms). Our analysis shows that first-line IMT (i.e., corticosteroids, IgEV, or PLEX) was generally effective in AE treatment, as only a few cases needed a second-line approach. Seizures were well-controlled with a single ASM in most of the cases. Conversely to the general seizure management in AE, sodium channel blockers were very seldom the first therapeutic choice during pregnancy. Levetiracetam was instead the most prescribed ASM. This evidence supports the need to avoid the teratogenic risk related to specific ASM (e.g., carbamazepine and sodium valproate) in favor of those with a safer profile during pregnancy (e.g., levetiracetam and lamotrigine). SE occurred in several cases, and second-line treatment with ASM was generally requested. Antipsychotic treatment was seldom employed. This interesting finding may be related to the low-to-moderate gravity of the symptoms or the fear of drug-related teratogenic effects.

Our analysis shows that maternal short-term clinical outcomes are most of the time favorable. However, the rate of miscarriage seems to be higher in women with AE. In fact, though the miscarriage pooled risk in general population has been estimated up to 16%,[56] it has been reported in about one in four women with AE. The rate of miscarriage was higher in women who received the diagnosis of AE during the first trimester. This intriguing finding may be explained according to the possible teratogenic effects of AE-related autoantibodies which can cross the placental filter and alter the physiological fetal growth.

According to the long-term evaluation, residual neurological symptoms (i.e., mild to moderate cognitive impairment) have been described in the affected women. This data is in line with previous studies focusing on long-term consequences of AE in general population.[57]

We did not identify any risk factor associated with increased fetal or maternal mortality. Neither clinical features (i.e., type of autoantibody, severity of neurological/neuropsychiatric symptoms, diagnosis of malignancy, status epilepticus) nor specific diagnostic procedures (i.e., CT or MRI scans with or without contrast) and treatments (i.e., ASMs, APT, or immunosuppressant drugs) were associated with worsen fetal or maternal clinical outcomes. Thus, no definitive conclusions can be reached according to the current evidence. Noteworthy, our analysis shows that maternal and newborn short-term clinical outcomes are most of the time favorable. On the contrary, the long-term evaluation shows residual neurological symptoms (i.e., mild to moderate cognitive impairment) in the affected women. No specific information regarding the long-term outcome of the newborns is available in most of the included studies.

Some recommendations should be kept in mind to reduce the teratogenic risk and worse fetal outcomes in AE during pregnancy. In the following sections, we summarized the available information regarding the treatment approach to AE, focusing on the associated teratogenic risk.

4.1 | ASM treatment and teratogenic risk

Even though seizures in AE are characteristically resistant to ASMs, these drugs maintain a role in symptomatic management, especially in those patients with focal-to-bilateral tonic–clonic seizures.[58,59]

A recent retrospective study demonstrated a considerably higher efficacy of sodium channel-blocking compounds to produce seizure freedom in AE patients.[60] However, the use of antiseizure treatments during pregnancy should be considered with caution, especially due

to the well-documented teratogenic and toxic effects associated with certain ASMs.

Evidence indicates that women with epilepsy (WWE) may have twice the risk of major congenital malformations (MCMs) compared to the general population (4%–6%), depending on the type and dose of the ASMs. Most accurate data on teratogenic risks are obtained from large pregnancy registers: The North American Antiepileptic Drug and Pregnancy Registry (NAAPR),[61] the United Kingdom and Ireland Epilepsy and Pregnancy Register (UKIEPR),[60] and the International Registry of Antiepileptic Drugs and Pregnancy (EURAP).[62] The highest MCMs risk seems to be associated with old-generation AMS like phenytoin (PHT), phenobarbital (PB), and valproic Acid (VPA). According to the international registries, PHT is associated with a 2.6%–6.4% risk of MCMs with a specific teratogenic risk for cardiac, cleft palate, and club foot. Similarly, PB is associated with a teratogenic risk in 5.5%–6.5% of the exposures, especially when administered at a dose higher than 80 mg/day. Finally, VPA is associated with MCMs in 6.7%–10.3% of the exposures and bears a specific teratogenic risk for hypospadias, cleft palate, club foot, neural tube defects, oro-facial/craniofacial, skeletal, and limb malformations.[63] Furthermore, VPA is associated with the "fetal valproate syndrome", a non-dose-dependent condition that is characterized by the development of facial dysmorphic and minor skeletal abnormalities.[63,64] Above all, it carries an intrinsic risk for neurocognitive impairment of children who can exhibit reduced IQ, memory, attention, or language skills compared with nonexposed ones.[65] On the other hand, newer ASM generations have a safer teratogenic profile. LEV and LMT seem to carry the lowest teratogenic risk. LEV bears a 0.7%–2.8% risk for MCMs and has no negative impact on neurocognitive development.[60,62,63–66] LMT instead is associated with a 1.9%–2.6% teratogenic risk, with a statistically significant dose-dependent effect.[60,62,63–66] LMT also seems safe concerning the long-term outcome and neurocognitive profile of children exposed to the drug in utero.[66,67]

Regarding sodium channel blockers, the MCMs prevalence with carbamazepine (CBZ) monotherapy varies from 2.6% to 5.5%, with a specific risk for microcephaly and a small fetus for gestational age (SGA).[60,62,63–66] In addition, intrauterine exposure to CBZ may be a risk for decreased verbal reasoning, as revealed by fetal antiepileptic drug exposure, and associated cognitive outcomes (NEAD) study.[67] Compared to CBZ, oxcarbazepine (OXC) presents a safer profile with an MCM risk that varies between 1.6% and 3%.[60,62–66]

Few data are available for the MCMs risk associated with lacosamide (LCS) administration. However, according to the NAAPR registry, LCS shows a safe pregnancy profile with no MCMs reported so far.[66] We want to stress that lacosamide add-on therapy and immunotherapy successfully produced freedom from seizures. Hence, considering the low rate of MCM and pregnancy complications, lacosamide is a safe and effective treatment option for AE-associated seizures in the context of pregnancy.

4.2 | Immunological treatment and teratogenic risk

IMT remains the most effective treatment for AE. According to the current guideline, IMT follows a stepwise approach of two lines treatment. The first line consists of corticosteroids (CS), intravenous immunoglobulins (IVIg), or plasmapheresis (PLEX), alone or in combination. When an adequate clinical response is not obtained, a second-line treatment (i.e., azathioprine, mycophenolate mofetil, cyclophosphamide, or rituximab) can be evaluated. The teratogenic risk associated with all these treatments can vary according to the specific type.

4.2.1 | First-line immunomodulant treatment

Treatment with CS seems to be safe during pregnancy. Pregnant women receiving corticosteroids usually show a low risk of developing MCMs, even though premature rupture of amniotic membranes and low birth weight babies may occur.[68] In addition, some authors indicated an increased risk of preterm birth, small for gestational age, low birth weight, intrauterine growth restriction, and neonatal intensive care unit (NICU) admission.[69]

Reports describing the use of PLEX during pregnancy are limited. However, consensus reports suggest that plasmapheresis is safe and appropriate, especially in patients who have failed other immunomodulatory treatments.[70,71] PLEX can be used safely during pregnancy with the proper training of a multidisciplinary team.

The safety profile of IVIg administration during pregnancy has been shown by several observational studies.[72] According to the literature, fetuses exposed to IVIg during pregnancy are not associated with any risks of MCMs or fetal distress. However, a mild risk of maternal hypertension has been described without interfering with the pregnancy outcome. It must be pointed out that IVIg might also play a protective role on the fetus due to the blockage of transplacental transfer of AE-associated IgG antibodies.[73]

4.2.2 | Second-line immunomodulant treatment

Azathioprine (AZA) is an antimetabolite frequently used in AE treatment. In a recent large cohort study,[74] the risk of developing MCMs after AZA treatment has been assessed to 4.4% compared to the 3.2% in the non-treated population. However, the adjusted statistical analysis revealed no significant differences between the two groups, except for the risk of ventricular and atrial septal defects, which was more frequent in the AZA group. In addition, data showed that preterm newborns and low birth weight were more frequently observed in patients treated with AZA. However, it is difficult to ascertain if these effects were due to AZA administration or to the effects of the specific underlying autoimmune disorder for which patients were treated.[74]

Mycophenolate mofetil (MMF) is an antimetabolite which is effective in the treatment of AE. MMF use during pregnancy has been associated with an increased risk of MCMs and pregnancy loss.[75] According to the literature, the risk of malformation is up to 26.7%, with external ear and facial dysmorphisms as the most described. In addition, kidney, heart, limb, and diaphragmatic malformations have been less frequently observed.[75] In line with this evidence, the current recommendations suggest avoiding MMF treatment during pregnancy.

Cyclophosphamide (CPM) is an alkylating agent that causes DNA–DNA cross-linking, enabling cell replication. According to the literature, first-trimester exposure to CPM can frequently lead to MCMs in the context of the so-called "cyclophosphamide embryopathy" characterized by multiple malformations (i.e., growth restriction, ear and facial abnormalities, absence of digits, and hypoplastic limbs).[76] However, some reports claim the possible safe profile and absence of MCMs after exposition to CPM in the first trimester of pregnancy. On the other hand, second and third trimester exposure appears to be less harmful to the fetus.[77] The long-term effects of gestational exposure to CPM are unknown. However, follow-up data available up to 4.5 years demonstrates that children do not present any sequela, though the risk of development of malignancies, immune deficiencies, or infertility in later age is unknown.

Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody that exerts its immunomodulant activity through B-cell depletion. According to the literature, the overall rate of spontaneous abortions and preterm born is 12%, and 41%, respectively.[78] On the other hand, MCMs were reported in a minority of cases.[78] The most frequent associated adverse effect was a transient low neonatal B-cell count with improvement after 6 months.

4.3 | Antipsychotics and teratogenic risk

Antipsychotic therapy (APT) is often required to manage behavioral symptoms of AE. The use of atypical antipsychotics (e.g., quetiapine, aripiprazole, olanzapine, clozapine, risperidone, and paliperidone) is typically preferred due to the fewer adverse effects. In addition, quetiapine, aripiprazole, and olanzapine show overall great safety in terms of fetal and neonatal toxicity, whereas risperidone and paliperidone carry a slightly increased teratogenic risk.[79] Insufficient information on clozapine is currently available to draw any conclusion. Indirect side effects might be carried by clozapine, quetiapine, and olanzapine, which increase the risk of gestational diabetes, an effect only partially explained by weight gain. Nonetheless, gestational diabetes is linked to large dimensions of the fetus for the gestational age, which may result in prematurity, dystocia, or other complications.

However, some concerns arose about the long-term effects of these drugs on the fetus' neurodevelopment. Interestingly, the increased risk of neurodevelopmental disorders found in children prenatally exposed to antipsychotics seemed more linked to other maternal features (e.g., age and comorbidities), and not to an iatrogenic effect, with the only exception of aripiprazole.[80] Furthermore, the offspring shows no significant changes in scholastic performances at standardized language and mathematics tests in the subsequent years. Thus, atypical APT do not significantly affect the development of these cognitive functions.

5 | LIMITATIONS

This study has several limitations. First, we acknowledge that publication as well as reporting biases may have influenced our results. In addition, the quality of the included studies was rated as low-intermediate according to NOS evaluation given most included articles consisted of case reports and case-series. Several information such as the time interval between the AE onset and the treatment start, and the IMT duration were not available in the included article, thus it was not possible analyze the impact of these variable on the maternal/fetal outcome.

6 | CONCLUSIONS

The diagnosis and treatment of AE during pregnancy are challenging. Caution should be paid to the potential teratogenic effects of several medical and instrumental interventions. The maternal and fetal clinical outcomes are most of the time favorable. Nevertheless, the rate of

miscarriage seems to be higher in women with AE. In addition, mothers may show long-term neurological deficits.

AUTHOR CONTRIBUTIONS

F.D. contributed to the conception and design of the study. M.T., G.E., S.C., M.R., J.L., B.N., F.R., M.D.P., L.T., S.T., D.C., M.D., V.P., and F.N. applied eligibility criteria and selected studies for inclusion in the systematic review. C.V. and J.L. performed the statistical analysis. F.D., M.T., G.E., S.C., M.R., and S.L.S. wrote the article and supervised all the data. All authors contributed to article revisions, read, and approved the submitted version.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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