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Pregnancy and delivery in anti-NMDA receptor encephalitis survivors

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Practical Implications

Successful pregnancy may follow anti-NMDA receptor encephalitis, but it is uncertain whether pregnancy is a risk for relapse in anti-NMDA receptor encephalitis survivors of reproductive age.

Anti-NMDA receptor (anti-NMDAR) encephalitis frequently develops in young women,[1] and several reports are available regarding anti-NMDAR encephalitis that is triggered by pregnancy or delivery.[2] Anti-NMDAR encephalitis accounts for 4% of all encephalitis cases,[3] indicating that it might be the most frequent cause of encephalitis in young women. Although its early symptoms, such as long-lasting consciousness disturbance or central hypoventilation, are often life-threatening, the majority of patients can recover completely with appropriate treatment.[1] Female survivors of reproductive age may be apprehensive about pregnancy, although it remains unclear whether pregnancy is a risk factor for the relapse of anti-NMDAR encephalitis. Here we report 2 patients with successful pregnancies and deliveries after a substantial recovery from anti-NMDAR encephalitis.

Case reports

Patient 1 is a 25-year-old woman, 9 weeks pregnant, who presented with a change in consciousness. She had a past history of a teratoma and underwent a right hemiovarian resection at age 17. She presented with athetosis-like involuntary movement and hypoventilation, which required mechanical ventilation and a tracheostomy. Because she remained in a coma for longer than 3 months, her parents and partner gave up continuing her pregnancy, and the pregnancy was terminated. A relapse of the teratoma was not identified at that time. Six months later, the patient began to recover after several courses of IV pulse methylprednisolone and oral prednisolone therapies. She had fully recovered 12 months after symptom onset. Anti-NMDAR antibodies were detected in her serum at onset, and anti-NMDAR encephalitis was diagnosed. Because a new teratoma in the left ovary was identified on a follow-up MRI, she underwent a partial ovarian resection at age 27. The pathologic diagnosis was a mature cystic teratoma with focal lymphocytic infiltration. Although recurrence of the tumor was detected at age 29, at age 30 she was married to a different man and became pregnant. The pregnancy course was unremarkable, and she had a normal delivery at 39 weeks of gestation. The newborn was neurologically and developmentally normal.

Patient 2 (prepregnancy history was previously reported in reference 4 [case 8]) is a 31-year-old woman who developed pyrexia and headache followed by a confused state and abnormal behavior. Subsequently, a stupor state, oral dyskinesia, and athetosis-like involuntary movements of the left arm developed. The stupor state continued for 2 months. IV pulse methylprednisolone and oral prednisolone were administered, and she had completely recovered by 3 months after onset. She had a history of left hemiparesthesia (age 27) and oculomotor palsy (age 28), and atypical multiple sclerosis was diagnosed based on multiple brainstem lesions

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Table Anti-NMDA receptor encephalitis associated with pregnancy and delivery

Reference	Age, y	Onset of encephalitis symptoms	Teratoma	Treatment	Outcome of mother	Fetal/neonate outcome
2	19	14th wk of gestation	+	Steroids, IVIg, PE	No sequela	No sequela
	20	8th wk of gestation	+	Steroids, IVIg		Terminated
	19[a]	17th wk of gestation	No	Steroids	No sequela	No sequela
5	29	8 wks after delivery	+	Steroids, PE, rituximab	No sequela	
6	24	5 y before pregnancy and maintained by IVIg	No	None	Worsening of spasticity 2 mo after delivery	Torticollis and strabismus at 4 mo and 6 mo
7	32	14th wk of gestation	+	IVIg, PE, AZP	No sequela	No sequela
8	25	3 mo after delivery	+	IVIg	No sequela	
9	23	1st trimester of pregnancy	+	Steroids, PE, rituximab		Miscarriage
10	26	22th wk of gestation	No	Steroids, PE	No sequela	No sequela
Patient 1	25	9th wk of 1st pregnancy	+	Steroids		Terminated
	30		+	None	No sequela	No sequela
Patient 2	36[b]	5 y before pregnancy	No	None	No sequela	No sequela

Abbreviations: AZP = azathioprine; IVIg = IV immunoglobulin therapy; PE = plasma exchange.
[a] Described in reference 13 in Japanese.
[b] Prepregnancy history was described in references 4 and 14.

observed on MRI. Between ages 32 and 34, she presented with 3 clinical relapses, including a disturbance of consciousness, right-hand clumsiness, motor aphasia, and dysphagia with or without brain lesions on MRI, which resolved after several administrations of IV methylprednisolone and plasma exchange. Oral azathioprine was added as a maintenance therapy. No teratomas were identified throughout the therapy course. Her serum was positive for anti-NMDAR antibodies but negative for anti-aquaporin-4 antibodies. Eventually, anti-NMDAR encephalitis overlapping a demyelinating syndrome was diagnosed.[4] After cessation of azathioprine, she became pregnant at age 36. She delivered via cesarean section at 35 weeks of gestation without any troubles. The newborn was neurologically and developmentally normal.

DISCUSSION

Anti-NMDAR encephalitis associated with pregnancy has been increasingly reported (table).[2,5–10] Symptom recovery after delivery, spontaneous improvement during pregnancy, or development during the postpartum period suggests the potential role of hormonal[2] or immunomodulatory effects of pregnancy. Most of the reported cases showed no sequela for mothers and newborns, except for 1 baby who presented with torticollis and strabismus.[6] However, the first pregnancy in patient 1 was terminated, and 2 of the 7 reported cases experienced a miscarriage or had an abortion (table). In multiple sclerosis[11] and rheumatoid arthritis,[12] pregnancy has a protective effect via pregnancy-induced changes in brain metabolism or cytokine responses.[11] Conversely, in patients with lupus, pregnancy could worsen the condition and may even be life-threatening for mothers and newborns.[12]

Patient 1 had a history of an ovarian teratoma, and the first pregnancy might have triggered the development of anti-NMDAR encephalitis. In addition, the ovarian tumor recurred before the second pregnancy. Patient 2 had anti-NMDAR encephalitis overlapping a demyelinating syndrome with 6 relapses. Relapse during the pregnancy was a potential concern. In our patients, the pregnancies and deliveries did not influence their course of illness, suggesting that

the history of anti-NMDAR encephalitis did not adversely affect the reproductive goals of these patients. In contrast, previous reports have suggested that pregnancy is a potential trigger of anti-NMDAR encephalitis, and 1 large cohort indicated that 12% of the patients relapsed.[1]

Both case reports (and a review of the literature) suggest that successful pregnancy may follow anti-NMDAR encephalitis. Future prospective studies are required to better understand the interacting risks of pregnancy and anti-NMDAR encephalitis. Future studies should also consider the factors that predict pregnancy outcomes in anti-NMDAR encephalitis.

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