A Rare Case of Refractory Status Epilepticus Recurring in the Second and Third Trimesters of Pregnancy

ABSTRACT Refractory status epilepticus (RSE) is a rare life-threatening neurological emergency, where the seizure activity cannot be stopped despite the use of at least two antiepileptic agents including intravenous (IV) benzodiazepines. Anesthetic drugs are used in the treatment of RSE. Midazolam is generally preferred as first-line anesthetic agent for treatment. There are a limited number of reported cases of RSE in pregnancy in the literature. Herein, we present a rare case of a patient who was intubated in the intensive care unit in two different periods of pregnancy (25th and 31st gestational weeks) due to recurrent RSE attacks resistant to midazolam.

Keywords: Status epilepticus; pregnancy; midazolam

Epilepsy is one of the most common neurological disorder which is also seen in pregnancy and has high maternal-fetal mortality and morbidity risks. Status epilepticus (SE) is characterized by a seizure lasts longer than 5 minutes or when two or more seizures occur together without returning to neurological basal situation between seizures. The incidence of SE is around 12.6/100,000. Refractory status epilepticus (RSE) is defined as persistent seizures despite the use of two intravenous (IV) antiepileptics including benzodiazepine. IV anesthetic agents are used in the treatment of RSE. Midazolam is commonly used for the treatment of RSE. Approximately 31-43% of SE episodes progress to the refractor status. Status epilepticus in pregnancy is very rare, and there are only a few reported cases of RSE during pregnancy. Herein, we present a rare case of a patient who was intubated twice with an interval of 6 weeks (at the 25th and 31st gestational weeks) due to recurrent RSE attacks resistant to IV midazolam.

CASE REPORT

A 23 year-old gravida 2, parity 1 pregnant woman with epilepsy who had ceased the use of antiepileptic drugs at the beginning of pregnancy was admitted to our hospital for routine pregnancy follow-up at 25th gestational week. She had a generalized tonic clonic seizure (GTCS) during her examination at the hospital. Although IV diazepam and levetiracetam were used, seizures persisted. The patient was admitted to the intensive care unit (ICU)
and after administration of IV midazolam, she was intubated. Phenytoin sodium infusion, levetiracetam, betamethasone were added to the treatment. Since the seizures recurred despite midazolam, thiopental sodium was administered. Obstetric ultrasonography (USG) examination revealed no problem, and the laboratory tests and blood pressure-pulse follow-ups were normal. Due to normal hematological parameters and stable blood pressures, eclampsia was excluded. The patient was intubated for four days in the ICU and then transferred to the obstetric service. The cranial magnetic resonance imaging (MRI) and diffusion MRI showed no pathology. Since her general condition was well and no problems were observed in her follow-up, she was discharged with oral antiepileptic (levetiracetam and carbamazepine) treatments. At the 31st gestational week, she applied to the hospital with vaginal bleeding. During medical examination, GTCS attacks began. The seizures persisted despite administration of IV diazepam and levetiracetam, so she was taken to the ICU and intubated with IV midazolam. But GTCSs did not stop despite IV midazolam and intubation. Therefore thiopental sodium infusion, IV levetiracetam, phenytoin and carbamazepine were added to the treatment. Her electroencephalography (EEG) showed slow waves with spikes of 5-6 Hz mixed with ground rhythm in both frontotemporal regions. Obstetric USG examination revealed that amnion fluid was sufficient, fetal measures were consistent with gestational week, materno-fetal Doppler findings were normal and placenta was intact. Non-stress test (NST) was reactive and also hemo gram, routine biochemistry, urine tests and vital parameters (blood pressure, pulse, fever) were normal. Cranial MRI revealed no problem. Vaginal examination revealed minimal vaginal bleeding. Rescue doze betamethasone was administered. On the second day in the ICU, because of non-reactivity and decreased variability in NST and vaginal bleeding, cesarean section was performed with general anesthesia. A 1826g and 46cm male infant with 1st minute Apgar score of 1 was delivered. The newborn was immediately intubated and transferred to newborn ICU. The patient, who had normal postoperative cranial computerized tomography, was extubated on the 2nd postoperative day. Her overall condition was stable, and she was discharged on the 6th postoperative day with oral antiepileptic agents while the newborn, who was followed in the ICU and developed pulmonary hemorrhage, was discharged on the 45th day of delivery. Written informed consent has been obtained from the patient for publishing this case.

**DISCUSSION**

Epilepsy is characterized by abnormal over-synchronized neuronal activity in the brain and may cause negative neurological, psychological, social and cognitive consequences. Status epilepticus is defined as continuous clinical or electrographic seizure activity lasting 5 minutes or more and/or recurrent episodes without recovery between these episodes. Status epilepticus is an emergency situation with high maternal and fetal mortality risks that is seen in 0-1.8% of epileptic pregnant women. Mortality rate of pregnant women with epilepsy is ten times more than those without it.

In 60% of SE cases, the seizures can be controlled with IV benzodiazepine and second-line anticonvulsant agents. If seizures continue despite those treatments, this is called as RSE. In patients with RSE, mortality risk reaches up to 40%. Generalized convulsive RSE is a life-threatening situation and has long-term adverse clinical consequences. The use of IV anesthetics acting at the inhibitory GABA-A receptors such as midazolam, propofol and thiopental/pentobarbital are necessary for treatment. In our patient, IV benzodiazepam and levetiracetam were used initially but the GTCSs continued. Therefore, the patient was considered as RSE. Then, IV midazolam was administered as the first-line anesthetic, and since the seizures persisted thiopental sodium was added to treatment as the second anesthetic agent.

The cause of SE is unclear in many cases. The etiology of SE includes central nervous system infections such as encephalitis, immunologic and cerebrovascular events (bleeding), neurodegenerative diseases, intracranial tumors, cortical dyspla-
sia, head traumas, intoxications, metabolic disorders (hypoglycemia, hyponatremia, severe hypocalcemia and hypomagnesemia), autoimmune diseases, discontinuing antiepileptic drugs or cutting down their doses. Management of RSE involves the treatment of underlying etiology in addition to IV anesthetics and antiepileptic drugs.3

One of the most important cause of epileptic seizures in pregnancy is the abrupt cessation of antiepileptic drug (AED) therapy by the pregnant woman.10 In our patient, the laboratory tests and intracranial imaging techniques did not show any pathology. Since there was no identified etiology, the treatment included only antiepileptic drugs and anesthetic agents. Although the patient had received valproate treatment for epilepsy, she discontinued antiepileptic drug therapy at the beginning of pregnancy due to possible teratogenic effects. We suggest that our patient’s clinical status impaired due to this condition.

Approximately one third of RSE cases return to the initial neurological status, while most cases have severe morbidity including short-term and long-term neurological problems.5 Generalized convulsive SE is accompanied by a marked increase in endogenous catecholamine release. This may result in arterial hypertension, potential lethal tachyarrhythmia, pulmonary edema requiring mechanical ventilation, renal damage, and disseminated intravascular coagulation. While the mortality risk is 3% in the first 30 minutes of generalized convulsive SE, this risk goes up to 19% after 30 minutes.5 During her follow-ups both in the ICU and obstetric service, our patient returned to her neurological basal status, and she had no complications related to endogenous catecholamine release.

While considering differential diagnosis for the seizures in pregnancy, eclampsia should be particularly taken into consideration. Eclampsia is characterized with the tonic-clonic seizures occurring in patients with preeclampsia. Preeclampsia and eclampsia generally occur after the second trimester of pregnancy.7 In our patient blood pressure follow-ups were stable, liver function tests and platelet values were within normal limits, there was no proteinuria, and she had a known history of epilepsy. Therefore we considered her GTCs as epileptic seizures. In addition, pregnant women with epilepsy have increased rates of pregnancy-related complications such as hypertensive disorder, bleeding in pregnancy, induction of labor, emergency cesarean section, postpartum hemorrhage and preterm birth.11 Our patient had vaginal bleeding with no cervical dilatation at the 31st gestational week and also the postpartum placenta examination did not show any ablation finding. Maternal tonic clonic seizures may present with fetal bradycardia and decreased short-term variability. These changes are considered to derive from fetal acidosis and hypoxia.10 Our patient had recurrent GTCSs, and the cause of decreased variability in non-stress test might be due to anesthetic agents in addition to fetal hypoxia.

During pregnancy the clearance of AEDs such as lamotrigine, phenytoin, carbamazepine, levetiracetam and oxcarbazepine increases and serum concentrations decrease. Therefore monitoring the plasma levels of these drugs throughout pregnancy is recommended. If the seizure frequency increases or free AED levels in serum decrease by 30% or more during pregnancy, it is recommended to increase AED doses.7 Our patient was discharged with oral antiepileptic agents after the first RSE attack. Serum drug levels could not be checked because she did not come for regular controls. The cause of recurrent RSE attacks at the 31st gestational week might be the possibility that the serum drug level did not reach the therapeutic level.

Management of SE in pregnancy depends on gestational week, etiology and additional comorbidities. In general, since recurring seizures may cause a serious risk both for the mother and the fetus, termination of pregnancy is recommended in RSE cases.12 In our case, after two RSE attacks, the pregnancy was terminated with cesarean section at the 31st gestational week. The patient’s condition improved at the postoperative period and seizures did not persist. Her pregnancy was not terminated at the 25th gestational week, when the first RSE attack occurred, because of pregnancy had just exceeded the
viability limit, the seizures were stopped with anesthetic agents, and her follow-ups did not show any problems.

In conclusion, RSE is a rare condition that threatens maternal and fetal life, and has short and long term complications. In epileptic pregnancies, discontinuation of antiepileptic treatment is one of the most important causes of seizures. Our patient had recurrent RSE attacks in different gestational weeks during pregnancy and these seizures were resistant to midazolam. In this regard, she is a rare case in the literature. In such cases, termination of pregnancy can be accepted as the most suitable treatment method in order to prevent both maternal and fetal complications.

**Source of Finance**

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

**Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

**Authorship Contributions**

This study is entirely author's own work and no other author contribution.

### REFERENCES