Seizures in Pregnancy

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KEYWORDS

• Seizure • Eclampsia • Epilepsy • Pregnancy • Antiepileptic drug

KEY POINTS

- Seizures during pregnancy pose significant maternal and fetal risks.
- The initial evaluation of seizures involves detailed clinical and physical examination histories, seizure classification, laboratory studies, and imaging interpretation.
- The management of epilepsy among women of reproductive age is complex and involves unique considerations during the preconception, antepartum, intrapartum, and postpartum periods.
- The management of the acute seizure during pregnancy should follow a predetermined algorithm with the presumptive diagnosis of eclampsia until proven otherwise.

INTRODUCTION: BACKGROUND AND EPIDEMIOLOGY

Seizures are the most common major neurologic complication encountered in pregnancy with a prevalence of in the United States of 1.2%.[1] Nearly one-half million women with epilepsy are of reproductive age and between 0.5% and 1.0% of all pregnancies occur among women with epilepsy.[2,3]

The etiology of seizures covers a wide range of diseases, vascular insults, infectious sequelae, malignant processes, metabolic derangements, toxic insults, primary central nervous system dysfunction, and more.[4,5] In pregnancy, eclampsia represents a unique consideration among possible causes of seizure. Although epileptic seizures are the most common, it is crucial to accurately determine the underlying cause of seizures in pregnancy to provide appropriate therapy.[4]

Epilepsy

Women with epilepsy who become pregnant are at a substantially increased risk of adverse outcomes, including preeclampsia, preterm labor, stillbirth, cesarean delivery, and a more than 10-fold increased risk of death.[6] The majority of maternal deaths

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are related to poor seizure control. As such, achieving control of maternal epilepsy is the primary concern in the management of pregnant women with an underlying seizure disorder.[3] This goal is complicated by the risk of potential congenital malformations owing to the use of antiepileptic therapy.[7–11]

DEFINITION AND CLASSIFICATION

Definition

Conceptually, an epileptic seizure is defined as "a transient occurrence of signs and/or symptoms owing to abnormal excessive or synchronous neuronal activity in the brain."[12] The clinical application of this definition is difficult, because it is often not possible to prove the presence of "abnormal excessive or synchronous neuronal activity." In addition, some seizures that are confirmed electrographically do not demonstrate detectable signs or symptoms.[13] To combat this issue, 3 separate operational definitions of epilepsy have been developed by the International League Against Epilepsy that can be more reasonably applied to the clinical setting:

1. At least 2 unprovoked seizures occurring greater than 24 hours apart,
2. One unprovoked seizure and the probability of further seizures similar to the general recurrence risk ($\geq$60%) after 2 unprovoked seizures, occurring over the next 10 years, and
3. Diagnosis of an epilepsy syndrome.[13,14]

Awareness of and recognition by providers that epilepsy represents a diverse array of brain diseases sharing the common presentation of seizure is critical. It is important for those providing pregnancy care to work closely with a neurologist to improve understanding of an individual's disease. This responsibility not only bears weighty implications for treatment, but also gives insight into predicting the character of the seizure disorder throughout pregnancy.[15,16] The resolution of epilepsy may be determined by a neurologist in the setting of women who have remained seizure free for the last 10 years, with the last 5 years off antiseizure medication, or individuals who were diagnosed with a childhood epilepsy syndrome who are now in adulthood.[14]

Classification System

The classification of epilepsy type greatly influences clinical management. In 2017, the International League Against Epilepsy developed a new classification system allowing for diagnosis at 3 levels according to the range of resources that may be available (**Fig. 1**).[17] In areas of resource-poor settings, diagnosis may be limited to level 1, whereas in settings of high diagnostic capabilities, a seizure can be considered among all levels of diagnosis.[17] Important changes include:

1. Extinction of the terms partial and complex, and instead only describing the presence of awareness;
2. The addition of a motor and nonmotor classification of focal seizures; and
3. The addition of a combined focal and generalized seizure category, and an unknown seizure type category.

Owing to the significant treatment implications, the International League Against Epilepsy also added 6 etiology subgroups to be considered among all levels of diagnosis. These subgroups are genetic, structural, metabolic, immune, infectious, and unknown.[17]

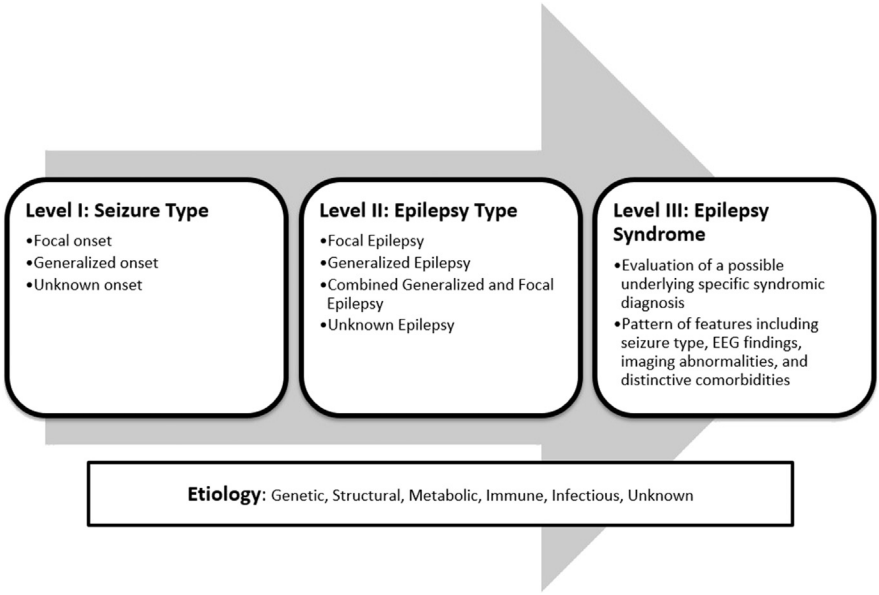

Fig. 1. The 2017 International League Against Epilepsy seizure classification system. EEG, electroencephalograph. (*Data from* Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58(4):512–21.)

INITIAL EVALUATION

The path toward diagnosis of a first seizure in a pregnant patient begins with a thorough history and physical examination. Although not always feasible, a detailed description of the event is helpful in both classifying the event as a seizure and to rule out differential diagnoses. This description includes possible triggers, behaviors, and postictal symptoms, if present. Attempts should also be made to uncover past episodes and underlying risk factors such as medications, poisonings, medical comorbidities, or genetic predispositions.[4,13] In patients suffering from a true epileptic event, the physical examination is typically normal, but it can be a critical component when there is concern for central nervous system bleeding, infarction, or infection. A thorough neurologic examination is important to evaluate upper or lower motor neuron signs and lateralizing lesions.[13]

Adjuvant laboratory tests and imaging are obligatory elements of the evaluation of a seizure to examine triggering factors and guide next steps in management.[18] Although not routinely recommended, the American Academy of Neurology (AAN) and the American Epilepsy Society state that blood counts, blood glucose, electrolyte panels, urinary analysis for protein, lumbar puncture, and toxicology studies may be helpful based on the clinical circumstances.[18] These 2 groups do advise routine electroencephalographic (EEG) and brain imaging with computed tomography (CT) scans or MRI as a part of the initial evaluation.[18] EEG is important for diagnosing the subtype of seizure, influencing therapy choice, and to predict seizure recurrence.[13,18] Between 8% and 50% of patients presenting with a first seizure will have a positive EEG demonstrating epileptiform abnormalities.[18] However, nearly 50% of patients who are clinically diagnosed with a seizure may have a normal EEG.[18] As such, a normal EEG

does not rule out the diagnosis of epileptic seizures. EEGs performed in the first 24 hours after a seizure or serial EEGs may prove to better aid in diagnosis and be more likely to demonstrate epileptiform abnormalities.[13] with regard to imaging, CT scanning is more commonly used in the acute workup of seizure owing to its quick availability compared with MRI.[4] Importantly, MRI is more sensitive for minor abnormalities common in focal and recurrent, unprovoked seizures.[13,18] Both CT scanning and MRI may diagnose an underlying brain tumor, stroke, infection, or other structural lesion.[4,18] Regarding the safety of CT scans in pregnancy, women should be made aware that the American College of Radiology states that the developing preembryo, embryo, or fetus is not at risk after receiving radiation exposure from a single diagnostic radiographic procedure.[19] During standard CT scanning of the head, the fetus is exposed to less than 1 rad of ionizing radiation.[19] An increase in fetal anomalies or pregnancy loss is not demonstrated in radiologic exposures of less than 5 rad.[20]

Throughout the initial evaluation, a broad differential diagnosis is appropriate (**Fig. 2**).[4,21,22] Neurovascular causes, cardiac causes, and metabolic conditions are

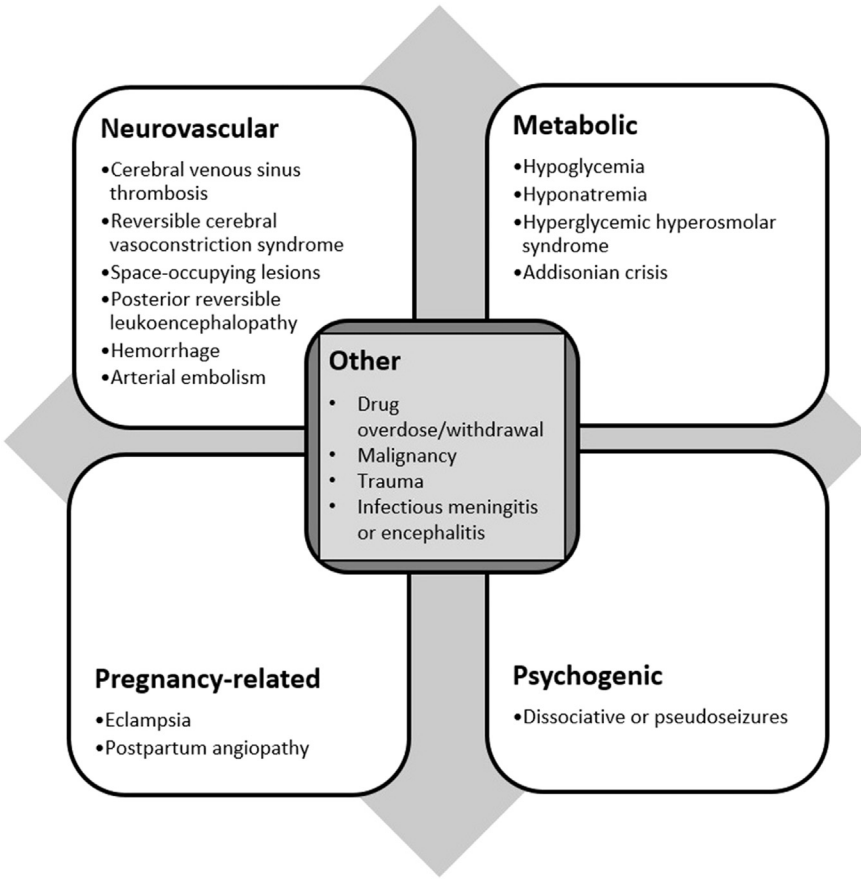

Fig. 2. Differential diagnosis of acute seizure. BP, blood pressure; CI, contraindication; DBP, diastolic blood pressure; EEG, electroencephalograph; HR, heart rate; ICU, intensive care unit; IM, intramuscular; IV, intravenous; OB, obstetrics; Pulse ox, pulse oxygenation; SBP, systolic blood pressure. (*Data from* Refs.[4,21,22])

all important considerations for first presentation of seizures in pregnancy.[4,21,22] Perhaps one of the most difficult diagnoses is that of psychogenic nonepileptic seizures, also called dissociative seizures or pseudoseizures, which are characterized by drug-resistant attacks.[13,22]

In addition to these differential diagnoses, the evaluation of seizure in pregnancy should begin with a consideration for eclampsia. Preeclampsia is defined as hypertension caused by pregnancy with the addition of end-organ involvement (proteinuria, thrombocytopenia, abnormal liver enzymes, elevated creatinine, or neurologic symptoms).[20] Eclampsia is defined as tonic–clonic seizures in the setting of preeclampsia.[20] Preeclampsia is generally seen in the later one-half of gestation and is more common with underlying chronic hypertension, diabetes, autoimmune disease (lupus), multiple gestation, and extremes of maternal age. Preeclampsia and eclampsia can occasionally be seen in early pregnancy in the setting of higher order multiple gestation, molar pregnancy, and severe maternal renal disease.[23,24] Unique to the initial evaluation of seizure in pregnancy is the consideration of fetal well-being. The management of women in whom preeclampsia and epilepsy are both potential etiologies of seizures of unknown etiology is discussed elsewhere in this article.

PRECONCEPTION COUNSELING AND MANAGEMENT

Preconception counseling is of utmost importance for all women of childbearing age who have epilepsy. Because many pregnancies are unplanned and changes initiated before conception and early in pregnancy can decrease adverse outcomes, the best time to begin preconception counseling is at disease diagnosis and the initiation of the first antiepileptic drug (AED).[15] Epilepsy is not a contraindication to pregnancy. Although the risk of fetal malformations is about double the risk of that in a nonepileptic woman, the absolute risk is still low, with a greater than 90% chance that she will have an uneventful pregnancy and a normal child.[15,25] If known risk factors exist for epilepsy inheritance, or if there is significant anxiety surrounding the possible inheritance of seizures, genetic counseling should be provided.[26] Components of preconception counseling include a discussion of contraception, maternal and fetal risks in pregnancy, selection and management of AEDs, and folate supplementation.

Contraception

Owing to induction of the hepatic cytochrome P-450 system, contraceptive failures in women taking oral contraceptives are increased if they are concomitantly taking AEDs.[27] Many of the most common AEDs fall into this category, including phenytoin, phenobarbital, carbamazepine, primidone, topiramate, oxcarbazepine, and to a lesser extent lamotrigine. As a result, the World Health Organization recommends that women choose long-acting reversible contraceptives such as the copper or levonorgestrel intrauterine devices and etonogestrel implants owing to their higher efficacy and lower drug interactions with AEDs.[27]

Maternal and Fetal Risks

Data regarding the effect of epilepsy during pregnancy on the mother and fetus are limited. A 2009 review by the AAN was not able to determine if an increased incidence of preeclampsia or gestational hypertension was present in women with epilepsy,[28] and they also concluded that preterm labor was only found to be increased in women who also smoked.[28] Many reports contained low case numbers, lack of adequate control groups, diversity among study methods, and absence of the influences of contributing social factors such as smoking and alcohol consumption.[15] In recent years,

however, larger population-based cohort studies and metaanalyses have shed light on relationships between maternal and fetal health and epilepsy (Table 1).[6,9–11,29–36]

Maternal complications

A population-based cohort study of 69,000 pregnant women with epilepsy were examined from 2007 to 2011[6] and a metaanalysis examining studies from January 1990 to January 2015 have provided risk estimates regarding maternal and fetal outcomes.[29] Among pregnant women with epilepsy compared with the general population, there is an increased risk of complications such as cesarean delivery (odds ratio [OR], 2.5), gestational hypertension (OR, 1.3), preeclampsia (OR, 1.6), antepartum hemorrhage (OR, 1.4), postpartum hemorrhage (OR, 1.8), preterm labor (OR, 1.5), and, most strikingly, maternal death with an overall adjusted OR of 11.5.[6] Results from the metaanalysis yielded additional findings of increased maternal risks of spontaneous miscarriage (OR, 1.5), preterm birth (OR, 1.16), and induction of labor (OR, 1.6).[29] Many of these risks were also cited in studies in Norway, Iceland, Canada, and Sweden, including the risks of preterm labor,[30] preeclampsia,[30–32] postpartum hemorrhage,[32,33] induction of labor,[31,34] and cesarean delivery.[30,32,35]

The increased risk of maternal mortality deserves requires further study.[3,6,15] Possible explanations include a higher percentage of contributing comorbidities, the overall increase of pregnancy-related life-threatening complications, an increase in seizure-related complications such as sudden unexpected death in epilepsy and status epilepticus, and a greater rate of depression and anxiety in these women.[37,38] The risk of mortality in pregnant women with epilepsy may be as high as 1 in 1000, a nearly 10-fold increase compared with women without epilepsy. The majority of these deaths are due to sudden unexpected death in epilepsy, which in turn is related to poor seizure control, highlighting the importance of continuing clinically indicated antiepileptic treatment throughout pregnancy and delivery.[3] The risk of developing status epilepticus is reported as 0% to 1.8%.[28]

Fetal complications

It is difficult to separate whether maternal epilepsy itself, or the effects of AED therapy, is to blame for many of the fetal and neonatal risks associated with these pregnancies. Studies still lack consistency regarding increased risk of perinatal death or stillbirth.[10,28,29] Women with epilepsy are more likely to have an infant who is small for gestational age[6,28] and with 1-minute Apgar scores of less than 7.[28] In addition, the

Table 1
Maternal and fetal complications in pregnancies affected by epilepsy

Maternal Complications	Fetal Complications
• Spontaneous miscarriage	• Small for gestational age
• Preterm labor	• 1-minute Apgar <7
• Preterm birth	• Perinatal death or stillbirth
• Antepartum hemorrhage	• Congenital malformations owing to AED use
• Gestational hypertension	• Adverse behavioral developmental and cognitive outcomes owing to AED use
• Preeclampsia	
• Induction of labor	
• Cesarean delivery	
• Postpartum hemorrhage	
• Maternal death	

Abbreviation: AED, antiepileptic drug.
Data from Refs.[6,9–11,29–36]

risk of spontaneous abortion in women taking AEDs is slightly increased compared with those not using medication.[39]

Current research suggests that fetal complications in epilepsy are related to the teratogenicity of AED rather than epilepsy itself.[7] The overall risk of fetal congenital malformations in women on anticonvulsant therapy ranges from 4% to 9% and depends greatly on the exact AED prescribed.[7] The overall risk for major congenital malformations is approximately 2.2% for carbamazepine, 3.2% for lamotrigine, 3.7% for phenytoin, and 6.2% for valproate.[8] Of all the AEDs, valproate has been shown to most consistently demonstrate a higher risk of congenital malformations as well as being associated with adverse behavioral developmental and cognitive outcomes.[15,36] In addition, polytherapy increased the overall risk of major congenital anomaly from 3.5% to 4.0% to 6% to 8% in 2 separate studies.[7,8] Common congenital malformations associated with specific AEDs are shown in **Table 2**.[4,15,25] Currently, the most commonly prescribed AEDs for women of reproductive age are lamotrigine and levetiracetam.[40] Women with epilepsy who have had a previous child with a congenital malformation have an increased risk of 16.8 per 100 births of having another child with a malformation.[41] In assessing the risk posed by antiepileptic therapy, it is important to recall that the baseline rate of fetal malformations in the general population is around 3%.[42,43]

Selection and Management of Antiepileptic Drugs

In epileptic women desiring pregnancy, a thorough history regarding the accuracy of seizure diagnosis, subtype, duration, frequency of seizure, and anticonvulsant use is essential. Most women with epilepsy will require continuing AED therapy. It is reasonable to wean AED therapy in patients who have been seizure free for 2 to 4 years.[15]

Table 2
Teratogenicity of antiepileptic drugs

Drug (Brand Name)	Rate of Teratogenicity (%)	Major Congenital Anomalies
Phenytoin (Dilantin)	0.7–7.0	Fetal hydantoin syndrome (cleft palate, hypoplasia of nails and distal phalanges), IUGR, cardiac malformations, NTDs, hypospadias
Carbamazepine (Tegretol)	2–6	Orofacial clefts, cardiac
Valproic Acid (Depakote)	4–14	Neural tube defects, orofacial clefts, Fetal valproate syndrome (limb abnormalities, cardiac malformations, fetal growth restriction, facial dysmorphology), polydactyly, craniosynostosis, hypospadias, poor cognitive and behavioral outcomes
Lamotrigine (lamictal)	2–5	Cleft lip and/or cleft palate
Levetiracetam (Keppra)	0–2	Nonspecific
Topiramate (Topamax)	3–4	Cleft lip and/or palate
Gabapentin (Neurotin)	0–6	Nonspecific
Phenobarbital	1–6	Cardiac malformations, oral clefts, poor cognitive outcomes

Abbreviations: IUGR, intrauterine growth restriction; NTD, neural tube defect.
Data from Refs.[4,15,25]

Because the frequency of seizure recurrence is greatest during the period immediately after the discontinuation of therapy, an attempt to wean anticonvulsant medication should ideally take place in the 9 to 12 months before attempting pregnancy.[28] During pregnancy, 20% to 30% of women will experience an increase in seizure frequency,[44] but those who are seizure free for at least 9 months before conception have an 84% to 92% likelihood to remain seizure free throughout pregnancy.[28] Overall, monotherapy is preferred over polytherapy owing to its lower risk for congenital malformations.[15,45] Similarly, a lower dose of anticonvulsant is preferred to a higher dose.[11] The teratogenic potential should also be considered with an attempt to avoid valproate and phenytoin if possible, with special efforts to avoid both valproate and carbamazepine in a patient with a family history of neural tube defects.[46] In an established pregnancy, it is generally best to continue an effective AED, even if teratogenic. The window for teratogenic effect is generally before the recognition of pregnancy; changing the regimen exposes the fetus to additional drug effects, and a change in therapy may precipitate seizures.[47]

Folate Supplementation

For all women of childbearing age, preconception folic acid supplementation of 0.4 mg/d is recommended to decrease the risk of neural tube defects in case of pregnancy.[46] Decreased first trimester maternal serum levels of folic acid in women with epilepsy are associated with an increased risk of congenital malformations.[48] Moreover, some AEDs decrease folic acid levels.[49] In women with epilepsy, the recommended dose of folic acid supplementation varies across guidelines. The 2009 AAN and American Epilepsy Society guidelines concluded that evidence was insufficient to determine whether a dose higher than 0.4 mg offers greater protection for women with epilepsy.[50] The American College of Obstetricians and Gynecologists, however, recommend 4 mg of folic acid daily for women at an increased risk of having a fetus with neural tube defects, including women on AEDs.[46] Higher doses of folate are not recommended because a dosage of more than 5 mg/d may be associated with delayed psychomotor development in offspring.[51]

ANTEPARTUM MANAGEMENT

Anticonvulsant Drug Monitoring

The main goal of pregnancy management is seizure prevention. Treatment for pregnancy complications that affect AED efficacy, such as nausea and vomiting, should be provided, stimuli causing seizures avoided, and medication compliance stressed.[52] As discussed, basic AED management principles include using monotherapy at the lowest effective dose as possible and avoidance of teratogenic AEDs.[15,45] Increased renal clearance, liver metabolism, and volume of distribution as well as decreased plasma protein binding and gastrointestinal absorption can affect anticonvulsant efficacy.[15,25] Recent AAN guidelines suggest that pregnancy produces a significant enough increase in clearance and decrease in the concentration of lamotrigine, phenytoin, carbamazepine, levetiracetam, and oxcarbazepine to warrant monitoring of plasma levels throughout pregnancy.[50] To identify the serum level that adequately controls seizures for the individual patient, measurement of a trough value of total and free concentrations of each AED should be performed before pregnancy or as early as possible in the first trimester.[25] This value can serve as a reference throughout the course of pregnancy. Some investigators suggest testing at weeks 5 to 6, week 10, and then once a trimester[53] Others suggest monthly monitoring.[15,25] As pregnancy progresses, the dose of AED should be increased for women who experience an

increase in seizure frequency or a decrease in the free level of the anticonvulsant drug of 30% or more.[25]

Vitamin K

Evidence regarding antenatal maternal administration of vitamin K is weak at best.[50] Historically, small studies suggested that mothers taking anticonvulsants with hepatic enzyme inducing properties (termed enzyme-inducing AEDs) may cross the placenta and cause degradation of vitamin K in the fetus, leading to hemorrhagic complications.[54–56] These enzyme-inducing AEDs included phenobarbital, phenytoin, carbamazepine, primidone, topiramate, eslicarbazepine, and oxcarbazepine. Indeed, infants of mothers taking AEDs have decreased levels of factors II, VII, IX, and X and normal values of factors V and VIII and fibrinogen,[54–56] a pattern indicative of vitamin K deficiency.[25] In 1993, a small case control study demonstrated increased vitamin K found in cord blood in women with epilepsy on AEDs and receiving vitamin K during the last month of pregnancy compared with mothers without supplementation.[57] Based on this study, some physicians routinely prescribe 10 mg/d of oral vitamin K to mothers on AEDs during the last month of pregnancy. Subsequent research has cast doubt on this practice. In 2002, an epidemiologic study examined 662 pregnancies of mothers taking AEDs without concomitant vitamin K supplementation and found no increase in bleeding complications in neonates.[58] All neonates received 1 mg vitamin K at birth, as is now standard practice.[58] Moreover, the AAN guidelines state that the evidence is insufficient to recommend for or against the practice of peripartum maternal vitamin K supplementation.[50] In the case that AED use does induce vitamin K deficiency in the neonate, routine vitamin K administration at birth seems sufficient to combat any adverse effects.[58]

Antepartum Testing

As in any pregnancy, early and accurate gestational dating is essential in the setting of epilepsy. According to the American College of Obstetricians and Gynecologists and the Society of Maternal Fetal Medicine guidelines, regardless of aneuploidy screening, an ultrasound examination at 11 to 14 weeks is recommended to confirm dates and screen for neural tube defects.[59–61] In cases of anencephaly, this approach provides the mother the option of terminating the pregnancy during the first trimester when this procedure is safest. In cases where termination is not pursued, early knowledge of a malformation can provide information important for later pregnancy planning. Because many centers may not be staffed with sonographers skilled in detailed first trimester ultrasound abnormalities, the first opportunity for screening for neural tube defects and other open defects may be approximately 15 to 22 weeks of gestation in the form of serum maternal alpha-fetoprotein.[62] At 18 to 22 weeks of gestation, women should undergo a detailed anatomic ultrasound examination to screen for neural tube defects as well as other malformations, such as cleft lip and palate, or heart anomalies with a maternal fetal medicine subspecialist.[59–61] When serum screening is combined with ultrasound examination, the detection rate of neural tube defects is between 94% and 100%.[63] Because fetal heart malformations are more common in women taking AEDs, a fetal echocardiogram is recommended between 18 and 22 weeks of gestation.[64] Antenatal testing is often performed empirically in women with epilepsy, although data are conflicting. Some authors have reported an increased risk of fetal growth restriction in epilepsy,[65] although others have not.[66] At this time, existing data are not sufficient to recommend definitively for or against ultrasound monitoring for fetal growth restriction in women with epilepsy. Studies are also conflicting in terms of the increased risk of stillbirth in the setting of epilepsy[6,27–29,66]

and, as such, there are insufficient data to recommend for or against antenatal testing in the setting of epilepsy in the absence of other comorbid medical conditions or fetal anomalies. In the setting of epilepsy complicated by fetal anomalies or other maternal conditions associated with stillbirth, antenatal testing is recommended.[67]

INTRAPARTUM CARE

Route of Delivery

Although epidemiologic data describe an increased risk of induction of labor[31,34] and cesarean delivery[30,32,35] for women with epilepsy, indications for the mode and timing of delivery in these women should follow routine obstetric practice. Cesarean delivery is not indicated simply for maternal epilepsy or AED use, except when seizures occur frequently during labor, when they are precipitated by physical activity, or when patients cannot cooperate during labor because of neurologic disorder or mental abnormality.[68] The vast majority of women will have successful vaginal deliveries.[69] There are no restrictions regarding regional anesthesia in the setting of epilepsy.[5,15,70] Regional anesthesia aids in decreasing stress levels, a known seizure precipitant, and reduces the risk for emergency general anesthesia induction when refractory seizures necessitate urgent delivery.[15,16] If general anesthesia becomes necessary, pethidine and ketamine should be avoided owing to their ability to lower seizure threshold, and sevoflurane should be avoided owing to its epileptogenic potential.[71]

Management of the Acute Seizure During Labor

Epileptic seizure

Women who have been on AEDs throughout pregnancy should continue during labor. Sudden cessation of anticonvulsant therapy or missed doses during a long labor course will predispose the patient to an acute seizure.[25] Overall, the risk of seizures during labor in women with epilepsy is 3.5% or less; these seizures are most likely to occur in women who had seizures during their pregnancy.[72,73] Other risk factors for seizures in labor include insomnia, pain, fatigue, and dehydration.[16] Women with recent convulsive seizures, recent seizures after stress or sleep deprivation, or a history of seizures in a previous labor may benefit from the use of a prophylactic benzodiazepine during labor.[16,74] Status epilepticus, which can be fatal to both the patient and her offspring, occurs in 0% to 1.8% of pregnancies in women with epilepsy.[28] In a small series of 29 patients, a total of 9 mothers and 14 fetuses died during or after an episode of status epilepticus.[75] A combination of fetal and maternal hypoxia and acidosis as well as changes in placental blood flow have been proposed as potential etiologies of maternal and fetal death in the setting of status epilepticus.[16,76,77]

Eclamptic seizure

Women with severe preeclampsia are at highest risk for developing eclampsia. In women with severe preeclampsia not receiving antiseizure prophylaxis, eclampsia occurs in 2% to 3% of cases compared with 0.6% of women with mild preeclampsia.[78] Owing to the increasing prevalence of hypertension disorders in pregnancy,[79] it is necessary to briefly discuss preeclampsia and eclamptic seizure. Risk factors for the development of preeclampsia include but are not limited to chronic hypertension, preeclampsia in a previous pregnancy, extremes of maternal age, renal disease, vascular disease, autoimmune disease, diabetes mellitus, and multifetal gestation.[80] A systematic review of more than 21,000 women with eclampsia demonstrated the most common preceding signs and symptoms of eclampsia are hypertension, headache, visual disturbances, right upper quadrant or epigastric

pain, and ankle clonus.[81] Occurring most commonly during the intrapartum and postpartum periods, maternal eclamptic seizure is most frequently manifested by generalized tonic–clonic seizures.[80]

Initial management considerations

As soon as a seizure (epileptic or eclamptic) is clinically recognized, the patient's medical stability should be assessed. Respiratory and circulatory status should be evaluated first, with supportive therapy such as oxygen or mechanical ventilation started if appropriate. Suctioning of secretions can be performed and maternal repositioning to the side should occur to increase blood supply to the placenta.[15] A seizure episode that occurs for the first time during pregnancy should be treated as eclampsia until proven otherwise.[15,25] The management principles specific to eclampsia include the use of magnesium sulfate for seizure control and antihypertensive agents to decrease stroke risk.[82–84] It is prudent to initiate intravenous or intramuscular magnesium sulfate if there is any suspicion for eclampsia. The superiority of magnesium sulfate as compared with phenytoin for eclamptic seizure management in terms of both prophylaxis and prevention of further seizure activity is well-established.[78,84,85] If seizures persist despite magnesium administration, benzodiazepines such as diazepam or lorazepam are a common choice for second-line therapy.[82] In this scenario, clinical suspicion for an underlying etiology beyond eclampsia would be increased. Importantly, the initial empiric treatment with benzodiazepines in the setting of a suspected eclamptic seizure should be avoided. The unnecessary addition of benzodiazepines coupled with the expected postictal state of the patient can obtund the patient and make it more difficult to protect the airway. Magnesium sulfate is absolutely contraindicated in patients with myasthenia gravis and, in patients with severe renal dysfunction, the dose should be adjusted or an alternative agent such as phenytoin used.[27,84,85] In a patient with known epilepsy, preeclampsia remains a likely cause of seizure. Management of epileptic and eclamptic seizure is summarized in **Fig. 3**.[82–84,86]

At the time of initial presentation, it may not be possible to differentiate between epileptic and eclamptic seizure. Although eclampsia is more common in the setting of hypertension, proteinuria, and patient report of headache, an eclamptic seizure can occur in a patient with only mild hypertension, no proteinuria, and no neurologic symptoms.[5,23,24] In addition, if the patient is unresponsive and records or family members are unavailable, it may not be possible to evaluate these factors.

Fetal heart rate monitoring

Maternal seizure activity is associated with uterine hypertonus and fetal bradycardia that, if present, can be treated with terbutaline by rapidly relaxing the uterus and improving fetal oxygenation.[16] Continuous fetal monitoring should be instituted if the fetus is at a viable gestational age. During or immediately after the seizure, fetal heart tracing abnormalities are common. Specifically, maternal hypoxemia may result in a loss of variability and a category II fetal tracing.[5] With prolonged maternal hypoxemia, fetal bradycardia and a category III fetal heart tracing may occur.[5] Fortunately, these findings typically resolve in 3 to 10 minutes.[5] However, the presence of fetal tachycardia and absent variability or sinusoidal pattern may suggest placental abruption and fetal anemia. In this case, preparations should be made to provide appropriate management of neonatal hypovolemia and maternal peripartum hemorrhage.[5] Management should focus on improving maternal oxygenation through treatment and prevention of future seizures and positioning and oxygen as noted.

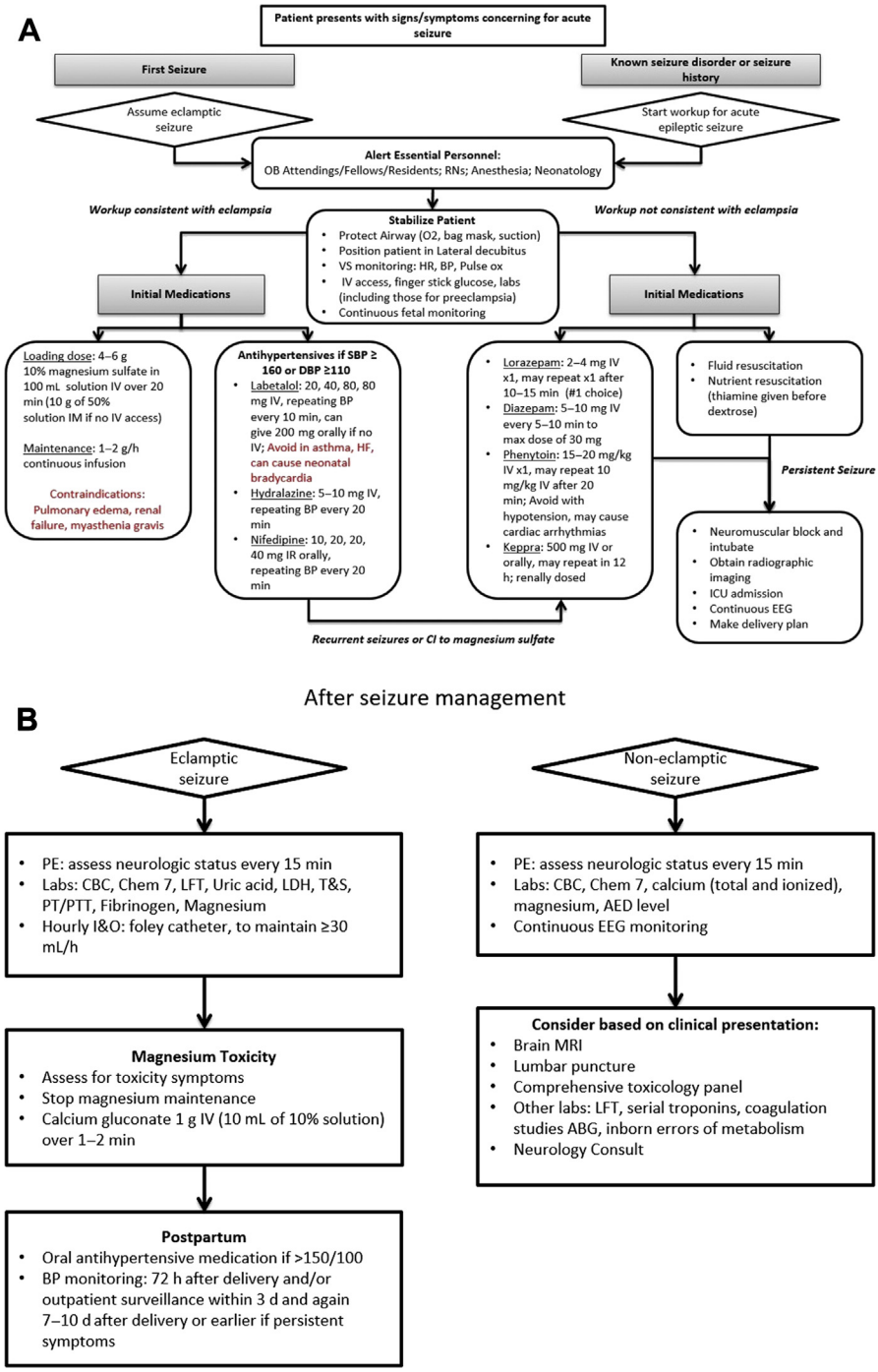

Fig. 3. (*A*, *B*) Intrapartum management of the acute seizure. (*Data from* Refs.[82–84,86])

Delivery

Although eclampsia is an indication for delivery at all gestational ages,[24] eclamptic seizure, even with fetal bradycardia, does not mandate immediate cesarean delivery.[5] To the contrary, attempting to transport an actively seizing patient to the operating room without controlling her seizures can compromise care and is generally discouraged.[5] Instead, further attempts at maternal and fetal stabilization, including the use of anticonvulsants, oxygen, antihypertensives, uterotonics, and maternal repositioning are recommended. However, if category III fetal heart tracing persists for 10 to 15 minutes despite resuscitative efforts, this may be a sign of placental abruption and immediate delivery should be considered.[5,15,16,80] In addition, women without improvement within 10 to 20 minutes of therapy initiation may benefit from an evaluation by a neurologist for consideration of other etiologies such as subarachnoid hemorrhage.[15] The time frame in which delivery should be undertaken is ultimately individualized in the setting of maternal seizure. Owing to the potential for administration of multiple benzodiazepines and AEDs, the neonatal care team should be notified of the potential for neonatal central nervous system depression.[16]

POSTPARTUM MANAGEMENT

Antiepileptic Drug Management

After delivery, active AED management is important, because the clearance and metabolism of these medications rapidly reverts to prepregnancy parameters. Most AED drug levels increase and plateau by 10 weeks postpartum,[87] but others, such as lamotrigine, increase rapidly, usually within 10 to 14 days.[4] If the dose was increased during gestation, the anticonvulsant dose should be tapered to that of prepregnancy levels or slightly higher over approximately 3 weeks. Changes in lamotrigine serum levels in particular increase quickly within the first week and dose reductions on postpartum days 3, 7, and 10 may be needed to prevent toxicity.[15,88] Above all, it is important that AED therapy is continued postpartum and that all mothers are monitored for signs of toxicity as dose alterations are made.

Safety in the Postpartum Period

The same vigilance over the antepartum and intrapartum safety of women with epilepsy should continue into the postpartum period because the 3-day peripartum period is the time of maximal seizure exacerbation.[89] All new mothers with epilepsy should be counseled on the importance of therapy compliance, signs of postpartum depression, and prevention of seizure triggers such lack of sleep and increased stress.[4,15] To prevent sleep deprivation, family members may need to help with night feedings to allow 6 to 8 hours of uninterrupted sleep. To counteract the likely increase in stress levels new mothers are bound to experience, AED dosage may need to be tapered to levels just above prepregnancy levels.[15] Further safety prevention measures that should be emphasized to the mother and family incorporate steps to protect the newborn in case of maternal seizure.[15] These measures include bathing the infant only when another caregiver is present, changing diapers on the floor instead of a changing table, using a stroller instead of a carrier that straps onto the mother, and avoiding stairs when possible.[4,15]

Breastfeeding

The benefits of breastfeeding are well-established.[90] All AEDs are measurable in breast milk in varying concentrations, but most experts agree that AED use does not preclude breastfeeding.[53,91] The NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study examined the cognitive outcomes of infants exposed to

carbamazepine, lamotrigine, phenytoin, and valproate. Investigators found no differences at 3 years of age in children exposed to all AEDs combined and for each individual AED group, but at 6 years the breastfed infants were found to have higher IQs and language scores than the infants of mothers who did not breastfeed.[92,93] Additional studies have demonstrated that the small amount of AED present in breast milk is eliminated with ingestion and not measurable in the neonatal plasma and supported the conclusion of the NEAD study that exposure to AED in breast milk does not seem to impede central nervous system development of the offspring.[94–97] Although not all confounding factors may have been accounted for in these studies and further prospective studies on AED exposure through breast milk are necessary, studies thus far are reassuring and support that benefits of breastfeeding while taking AED likely outweigh risks.

SUMMARY

Seizures remain among the most serious complications encountered in pregnancy. Both maternal and fetal risks associated with seizure management demand the need for comprehensive and standardized care both at time of initial diagnosis of a seizure disorder and throughout pregnancy. Counseling provided during the preconception, antepartum, intrapartum, and postpartum periods is essential in providing patient-centered care and to limit adverse pregnancy outcomes.

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