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Contemporary management of epilepsy in pregnancy

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Abstract

Purpose of review: The number of reproductive aged people with epilepsy in the United States is increasing, making epilepsy during pregnancy more prevalent. Simultaneously, more people are using newer generations of anti-seizure medications before, during, and after pregnancy. Here we review current evidence on contemporary management and outcomes of pregnancies among people with epilepsy.

Recent findings: This review evaluates recent literature to summarize current practices in pre-conception counseling, contraception, anti-seizure medications before, during and after pregnancy, and peri-partum and post-partum risks in people with epilepsy.

Summary: With the introduction of newer generation anti-seizure medications being used during pregnancy, current literature shows there may be decreased risk in adverse fetal and maternal outcomes. In the peri-partum and postpartum period, recent literature shows that people with epilepsy have increased risk of severe maternal morbidity and hospital readmission. Given this, as well as considerations for dosing of antiseizure medications, close surveillance of people with epilepsy during pregnancy is warranted.

Keywords

epilepsy; anti-seizure medications; high risk pregnancy; maternal morbidity

Introduction

Epilepsy is one of the most common neurologic conditions worldwide. About 1.2% of the U.S. population have active epilepsy, including about half a million females of reproductive age, with prevalence rising [1**]. Epilepsy affects about 0.3-0.8% of all pregnancies and is the most frequent major neurologic disorder in pregnancy [1**]. Over time, newer generation anti-seizure medications (ASMs), such as levetiracetam, lamotrigine, oxcarbazepine, topiramate, and clobazam, have been increasingly utilized

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Conflicts of interest

None

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in pregnancy. Meanwhile older generation ASMs, defined as bromides, phenobarbital, primidone, phenytoin, ethosuximide, carbamazepine, and valproate, are being used less. Given the increase in epilepsy diagnoses and recent shift towards utilization of newer generation ASMs, the focus of this review is on contemporary management of epilepsy before, during and after pregnancy.

Reproductive health counseling in people with epilepsy

If a person is engaged with neurologic care for their epilepsy, their neurologist may be the first healthcare provider to discuss pregnancy risks. In a survey of 208 child neurologists, 95% had discussed reproductive health with females with epilepsy at least once in the past, however, one-third did not discuss reproductive health routinely. [2*]. This counseling is especially important as many people with epilepsy are on ASMs, which can be teratogenic. The frequency of counseling on teratogenicity of ASMs by neurologists was estimated to be 86-100% in people taking ASMs for epilepsy [3*]. Additionally, for people with epilepsy, there may be up to a 3-fold increased risk for their children to have epilepsy compared to the generalized population, with increased risk if the diagnosis is related to a syndrome and relatively increased risk with generalized epilepsy compared to focal epilepsy [4]. There is also increased risk of epilepsy in children if there is maternal epilepsy, compared to paternal epilepsy [5*]. Clearly, it is prudent for people with epilepsy to receive appropriate reproductive counseling due to the possible effects on pregnancies, as will be discussed later.

Fertility

Prior studies on birth rates in people with epilepsy have had conflicting results, with some showing a lower birth rate and others showing no difference in birth rate compared to those without epilepsy [1**, 6**]. However, a lower birth rate does not necessarily mean lower fertility, as birth rates can be influenced by multiple psychosocial factors such as interpersonal relationships and desire to get pregnant. A study using United States Epilepsy Birth Control registry data showed a higher risk of infertility (9.2% vs 6.4%) and impaired fecundity (20.7% vs 12.7%), defined as people who were infertile or did not carry a pregnancy to a live birth, in people with epilepsy compared to the general population. There was no statistically significant difference in fertility or fecundity with use of ASMs [7]. Despite studies suggesting potential fertility impacts associated with epilepsy, it is important to remember that people with epilepsy are overall still a fertile population. Thus, in those who do not desire pregnancy, it is important to have appropriate contraceptive counseling.

Contraception

To ensure effective contraception in people with epilepsy, individualized assessments of contraception methods and ASM usage must be done. Some ASMs, such as phenytoin, phenobarbital, and carbamazepine, are inducers of the cytochrome $P_{450\ 3A4}$ (CYP3A4) enzyme, which decreases the circulating levels of hormones and thus, duration and efficacy of hormonal contraceptives [1**, 6**]. Newer ASMs such as topiramate, oxcarbazepine and felbamate are less potent CYP3A4 enzyme inducers but can cause selective reduction of progestin or estradiol levels. Additionally, some ASMs like lamotrigine have decreased circulating levels when hormonal contraceptives are used, requiring an increase in the

dose to maintain therapeutic levels [1**, 6**]. While there is no contraindication to any contraception method in people with epilepsy, obstetrician-gynecologists should develop an appropriate contraceptive plan in partnership with patients with epilepsy by considering their ASM regimen [8, 9].

Pre-conception counseling

When a person with epilepsy decides to pursue pregnancy or conceives, multi-disciplinary communication is needed between neurologists and obstetricians, preferably prior to conception. A retrospective study on planned and unplanned pregnancies in people with epilepsy showed that in planned pregnancies, people had less generalized tonic-clonic seizures ($p = 0.002$) and more people were seizure-free (41.0% vs 22.8%, $p < 0.001$) [10*]. Planned pregnancies also had decreased rates of induced abortions, preterm births, and major congenital malformations, and decreased risk of adverse fetal outcomes, likely due to optimization of ASM regimen, adequate follow-up, and folic acid supplementation [1**, 10*]. Recommendations of folic acid supplementation vary from 0.4 through 4-5mg per day [1**]. This highlights the importance of multidisciplinary planning for prenatal care among people with epilepsy to ensure that the person enters pregnancy with optimized seizure control and with adequate counseling regarding risks.

Antepartum considerations in people with epilepsy

Though the majority of pregnancies in people with epilepsy result in normal, uncomplicated births, they are considered high risk pregnancies due to increased obstetric and fetal risks. Prior literature shows that people with epilepsy are at higher risk for spontaneous abortion, antepartum hemorrhage, postpartum hemorrhage, gestational hypertension, pre-eclampsia, induction of labor, cesarean delivery, congenital malformations, preterm birth, fetal death, severe maternal morbidity, and maternal mortality during pregnancy [1**, 6**, 11, 12**, 13*]. The increase in risk for these complications remain relatively small, approximately 1-1.7-fold with the exception of maternal mortality, which has an increased risk up to 10-fold [14*].

In particular, etiologies of maternal mortality in people with epilepsy have been investigated given concern for sudden unexpected death in epilepsy (SUDEP), which occurs without apparent cause and regardless of pregnancy state or seizure control. Studies from Japan and Turkey both found that SUDEP was a leading cause for maternal deaths [13*, 15*]. SUDEP was also associated with a longer duration of epilepsy and longer time interval between last seizure and pregnancy [13*]. In maternal deaths in people with epilepsy where a cause was identified, leading reasons were pulmonary embolism (32%), cerebrovascular event (23%), and cerebral vein thrombosis (15%) [13*].

Other outcomes, such as cesarean birth, congenital malformations, and preterm birth, have previously been associated with exposure to ASMs [1**, 11]. However, a recent study by McElrath et al. found no difference in unlabored cesarean delivery in people with epilepsy despite exposure to ASM, type of ASM, monotherapy or polytherapy [12**]. Given scant to conflicting evidence, it remains unclear if the increased risk of these adverse obstetric outcomes is related to epilepsy, uncontrolled seizures, or ASMs, apart from major congenital

malformations which have been associated with ASMs and in some instances have biologic plausibility [1**]. Regardless, minimizing seizures during pregnancy in people with epilepsy using a multidisciplinary approach with close input by a neurologist should be prioritized.

Seizure frequency during pregnancy

Seizures are especially dangerous during pregnancy due to the risk of direct trauma, placental abruption, and potential harm to the fetus through hypoxemia and asphyxia leading to fetal heart rate decelerations [1**]. Prior studies show seizure frequency remains stable throughout pregnancy in most people with epilepsy, with increased seizures occurring in approximately one-third of pregnancies [1**, 4]. Increased frequency of seizures in pregnancy, especially tonic-clonic seizures, has been associated with cognitive delays in infants such as lower verbal IQ and developmental delay. Risk varies by type of seizure, with focal seizure unlikely to have a major impact on the fetus [1**].

Voinescu et al. found that lack of seizure freedom nine months prior to pregnancy was associated with an over 6-fold risk of increased seizure frequency during pregnancy [16**]. Higher risk of increased seizure worsening during pregnancy was also associated with people with focal epilepsy, particularly frontal lobe epilepsy, compared to generalized epilepsy. In addition, polytherapy compared to monotherapy had an 8-fold risk of seizure worsening, though this association could be confounded by indication if the patient requires higher levels of ASMs to achieve a stable disease state [16**]. This highlights the importance of optimizing ASM regimen to improve seizure control prior to pregnancy.

Anti-seizure medications during pregnancy

Most people with epilepsy use ASMs throughout pregnancy, often requiring close monitoring. Prior studies have noted that there is a decrease in circulating levels of ASMs during pregnancy, which can increase seizures if doses are not adjusted accordingly [1**]. A recent study showed that during pregnancy ASM concentrations were decreased significantly with increasing gestational age, and compared to postpartum, in specific ASMs (lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, lacosamide, and zonisamide) [17*]. These characterizations provide further evidence that ASM levels need to be checked frequently as doses may need to be increased during pregnancy or decreased in the postpartum period, depending on the specific ASM, to maintain a steady therapeutic level and prevent adverse clinical outcomes.

Newer generation anti-seizure medications

In an effort to improve seizure control and reduce teratogenic effects, newer ASMs have become more popular in pregnancy over the last two to three decades. Using data from the Kerala Registry of Epilepsy and Pregnancy to review prescribing patterns in India from 1998-2017, Keni et al. found that significantly less people were off ASMs (12.7%) in the more recent years, while the prevalence of monotherapy and polytherapy remained stable, around 61.5% and 25.8% respectively [18*]. Since the use of older ASMs (phenobarbitone, phenytoin, valproate) had declined significantly from 17.8%-23.7% to 5.4%-17.5%, while newer ASMs (clobazam, levetiracetam, lamotrigine, oxcarbazepine) had increased during

this time from approximately 0-0%-4.7%% to 5.5-40.5%, this indicates that newer ASMs may be more efficacious and better tolerated by patients. Occurrence of seizures during pregnancy significantly decreased with the shift towards newer ASMs [18*].

Major Congenital Malformations

Another benefit of newer ASM use during pregnancy is the decreased risk of major congenital malformations (MCMs) [18*]. People with epilepsy have a higher risk of having children with MCMs, most commonly cardiovascular defects, musculoskeletal defects, and spina bifida, in pregnancy [1**, 4, 19*]. Pregnant people with epilepsy should undergo an early anatomical ultrasound and testing of maternal serum alpha fetoprotein in attempt to detect these malformations. One major contributing factor to the development of MCMs that has garnered attention is exposure to ASMs, as the risk of MCMs appears to be similar in people with epilepsy not using ASMs compared to the general population (1.1-3.3% vs 2.1-2.9%). The mechanism of action is thought to be due to folic acid deficiency or conversion of ASMs to toxic, unstable metabolites [19*]. Valproate and carbamazepine have been independently associated with development of neural tube defects such as spina bifida, with prevalence of spina bifida with valproate estimated at 1-2%, 10-20 times the baseline rate, and 0.5% with carbamazepine [20]. Polytherapy, particularly with valproate, also had a significantly increased risk of overall MCM [1**, 4, 19*, 21*]. Due to significant risks with valproate, this should be avoided in pregnancy if possible.

Newer ASMs have decreased rates of MCMs compared to older ASMs, with some, such as lamotrigine, showing no difference in rates of MCM compared to the general population [1**, 21*]. Individual medications appear to have different risk profiles [18*]. Within newer ASMs, lamotrigine and levetiracetam appear to be relatively safer, with topiramate and clobazam having a higher potential teratogenicity profile though still lower than older ASMs [1**, 18*, 19*]. Topiramate has specifically been associated with oral cleft malformations [22*]. Vajda et al. examined the impact of ASM exposure and found that among carbamazepine, valproate, lamotrigine and topiramate, levetiracetam had the highest rate of having both a malformation-free and seizure-free pregnancy, though it was not statistically significant [23*]. Though overall newer ASMs appear to have decreased risk of overall MCMs, further research is needed to show the risk profiles of individual ASMs.

Neurodevelopmental outcomes

Another concern regarding the use of ASMs in pregnancy has been long-term neurodevelopmental outcomes in children with prenatal ASM exposure. Previously, lower IQ was noted in children with prenatal exposure to valproate or phenobarbital, while significant differences were not seen in children with prenatal exposure of carbamazepine, lamotrigine or phenytoin, showing that some newer ASMs have decreased risk of affecting long-term cognitive outcomes [1**]. Similarly, recent studies show no significant effects on cognitive outcomes of children up to two years old who have been exposed to lamotrigine and levetiracetam, though one study found lower motor and general adaptive scores in children exposed to higher maximum ASM levels in the third trimester [22*, 24*]. Though these studies are promising for safety of newer ASMs, further studies need to be done to establish long-term outcomes.

Peri-partum and Postpartum outcomes in people with epilepsy

While intrapartum, seizure burden may increase in 1-2% of pregnancies in people with epilepsy. Special care must be taken to prevent lowering the seizure threshold, such as by promoting adequate sleep during labor. When a seizure during labor occurs in someone with epilepsy, care should be taken to prevent self-harm to the person and the fetus by positioning the person on their side to maintain left lateral tilt and securing the environment with padding and bed rails. Airway and oxygenation must be maintained at all times. The seizure should be treated routinely with a quick-acting benzodiazepine, such as lorazepam or diazepam. In the case of epileptic seizures, magnesium sulfate is not an appropriate treatment, though it can be difficult to discern from eclampsia in someone without a known history of epilepsy, and thus in this case epilepsy and eclampsia should be treated simultaneously. Fetal bradycardia is expected and should be transient with treatment of the seizure, typically within 2.5-5 minutes depending on the type of seizure [25]. Rather than rushing to emergent cesarean delivery during a seizure, awaiting return of fetal heart rate is key and will often occur with improvement in maternal status. Due to risk of fetal harm during a seizure, if fetal heart rate tracing does not normalize after seizure recovery, cesarean delivery should be pursued if vaginal delivery is not imminent [1**, 25]. Epilepsy alone is not an indication for cesarean delivery [1**, 12**]. Overall, though most people with epilepsy will have an uncomplicated delivery, they remain at high risk for seizures and other complications.

Delivery outcomes

During delivery admission, people with epilepsy have been found to be more likely to develop hypertensive disorders (19% vs 12.9%, $p < 0.001$), preterm labor (7.3% vs 4.8%, $p < 0.001$), and severe maternal morbidity (SMM) events (3.2% vs 1.6%, $p < 0.001$) [26**]. The SMM composite includes 21 events, such as eclampsia and cardiac arrest, that occur during delivery hospitalization and result in significant consequences, as defined by the Centers for Disease Control and Prevention (CDC). Panelli et al. found a three-fold increased risk of SMM and four-fold increased risk of non-transfusion SMM in people with epilepsy compared to those without. When characterized by organ systems, all SMM indicators were significantly increased, particularly those related to hemorrhage and transfusion [27*]. Another study similarly found that people with epilepsy on ASMs during pregnancy had an increased risk of SMM to two-fold with transfusion and three-fold without. This risk was further increased in people with epilepsy not taking ASMs to almost six-fold with transfusion and eleven-fold without [28**]. It is possible that the lack of ASM use may indicate lack of seizure control during pregnancy, as seizures themselves can contribute to SMM events such as pulmonary edema or hemorrhage. While most people with epilepsy do not experience SMM, healthcare providers should be aware of these significantly increased risks when managing patients with epilepsy.

Postpartum complications

People with epilepsy are not only at higher risk of complications at delivery, but are also at increased risk for postpartum hospital readmission compared to those without epilepsy within 30 days (adjusted OR 1.86, 95% CI 1.66-2.08, $p < 0.001$) and 90 days (adjusted

OR 2.04, 95% CI 1.83-2.28, p < 0.001) of childbirth [26**]. Some reasons for increased readmission may be due to sleep deprivation and missed medication in the postpartum period, which can increase risk for seizures [1**]. People with epilepsy have been shown to have worse sleep quality during pregnancy and the postpartum period than people with epilepsy who were not pregnant [29*]. Additionally, people who had an increase in ASM dose during pregnancy may begin to taper back to pre-pregnancy dose postpartum, which can increase risk of seizure and requires close monitoring with a neurologist [14*]. People with epilepsy are also more likely to have peripartum depression and anxiety, which are associated with high seizure frequency [1**]. Additionally, another study showed that, compared to people without epilepsy, people with epilepsy had a ten-fold risk of readmission within 30 days of childbirth due to a psychiatric illness, with top indications for readmission being mood disorders, schizophrenia and other psychotic disorders, and substance-related disorders [30*]. These risks should be discussed with patients, and providers should ensure appropriate outpatient follow up to mitigate these risks.

Breastfeeding

In the postpartum period, the proportion of people with epilepsy who initiate breastfeeding is significantly lower compared to people without epilepsy (50.9% vs 87.6%), despite its benefits, including promoting bonding and decreasing risk of diabetes [1**, 4, 31*]. This may be related to potential concerns that exposure to ASMs through breast milk could affect child development; however, long term studies have shown no adverse effects of ASM exposure via breast milk at 3 years of age [1**]. People with epilepsy were more likely to initiate breastfeeding if they had a vaginal birth, lack of MCM in the child, or received antepartum counseling on breastfeeding. They were less likely to initiate breastfeeding if they had an older generation ASM monotherapy or polytherapy compared to no ASM treatment [32*]. They are also less likely to maintain breastfeeding at 6 weeks and 3 months postpartum; however, if they received postpartum consultation with a board-certified lactation consultant, they were more likely to continue breastfeeding at 6 weeks [31*]. With appropriate antepartum and postpartum counseling on breastfeeding, rates of breastfeeding in people with epilepsy can be improved.

Conclusion

In conclusion, in people with epilepsy, appropriate management and counseling by both neurologists and obstetrician-gynecologists are needed to achieve patients' goals, whether that is to prevent pregnancy or to safely conceive. During pregnancy, while the overlying objective is to minimize seizure frequency, usually with ASMs, this must be balanced with the associated teratogenic risks. Though recent studies appear to show increased seizure control and reduced risk of MCMs and cognitive outcomes with the use of newer ASMs during pregnancy, this review highlights the lack of available data.

Furthermore, this review also emphasizes the recent studies showing significantly increased risk for SMM events and postpartum hospital readmission in people with epilepsy. We advocate for additional research characterizing clinical outcomes when newer generation of ASMs are used during pregnancy to demonstrate their safety, as well as research identifying

risk factors for increased SMM in this population. In doing so, we hope to establish possible interventions to improve overall outcomes in pregnant people with epilepsy.

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KEY POINTS

- Though people with epilepsy have high risk pregnancies and should be monitored closely, with a multidisciplinary prenatal care approach, most pregnancies will not have adverse outcomes.
- Prior to and during pregnancy, multidisciplinary care with a neurologist will help optimize seizure control and clinical outcomes.
- The need for management of epilepsy should be balanced with the risks of anti-seizure medications, which appear to be decreased in newer generation anti-seizure medications though additional research is needed.
- People with epilepsy are at significantly increased risk for severe maternal morbidity, postpartum hospital readmission, and psychiatric illness. Future research addressing these factors may aid in risk reduction strategies.