Case: SEIZURES AND EPILEPSY IN PREGNANCY

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A 29 year old woman with a longstanding history of absence epilepsy since age 16 presents for pre-pregnancy counseling. Her seizures are characterized by staring spells lasting one minute duration, and she has been treated with lamotrigine extended release formulation 200mg/day. She has been seizure-free, to her knowledge, for at least 5 years. However, in the past, when she tried to discontinue lamotrigine, she had breakthrough seizures.

What pregnancy-related considerations warrant discussion with women with epilepsy who are of childbearing age? What important points should be discussed at this office visit with a patient presenting for preconception counseling?

All anticonvulsants, also known as antiepileptic drugs (AEDs), have been linked with major congenital malformations (MCMs) among offspring exposed in utero. However, seizures in pregnancy are also risky. Therefore, all women of childbearing age should be counseled on the possibility of birth defects and seizure-related risks, should they become pregnant.

Because 50% of pregnancies are unplanned, discussion of pregnancy concerns should occur in all women with epilepsy who are of childbearing age. This should include a candid discussion about folic acid supplementation as well as birth control methods. While birth control methods are often reviewed by obstetricians/gynecologists in routine office visits, it is important for specialists treating chronic diseases in women, including epilepsy, to gain comfort with contraception discussions, particularly in situations in which medications used to treat these conditions may have teratogenic implications, and where drug-drug interactions with hormone-based contraception may be a factor in unplanned pregnancies. This is certainly true for anticonvulsants. For example, combined hormonal contraceptive methods can lower lamotrigine levels due to glucuronidation. Other anticonvulsants that are hepatically metabolized through CYP450, and in particular, enzyme-inducing anticonvulsants like phenytoin, carbamazepine, topiramate, phenobarbital among others, can reduce levels of the exogenous hormones in the bloodstream. The downstream effect of increased enzyme induction makes hormone-based birth control less effective and increases the risk of unintended pregnancies. Long-term reversible birth control methods such as intrauterine devices and contraceptive implants have low rates of unintended pregnancies, and some of these methods have low likelihood of conflict with anticonvulsants.[i]

Are some anticonvulsants riskier in pregnancy than others?

Although anticonvulsants have known teratogenic risks, these drugs can be separated into low, intermediate or unknown, and high risk categories. Lamotrigine is among the safest anticonvulsants used in pregnancy, with a risk of MCMs of approximately 2.0% (compared to 1-2% of the general population). Levetiracetam is another common anticonvulsant used on pregnancy because of its relatively low risk of MCMs (2.4%).[ii] In spite of prior predictions, two older, hepatic enzyme inducing anticonvulsants had lower than expected rates of MCMs: phenytoin (2.9%) and carbamazepine (3.0%). It is worth noting that at the North American

Pregnancy Registry[iii] and other world-wide registries continue to enroll women with epilepsy, the exact numerical values of these rates, as well as confidence intervals, change. Higher risk anticonvulsants include valproic acid, phenobarbital, and topiramate. Phenobarbital carries a risk of MCMs of 5-6%, and Topiramate 4-5%. There is some evidence of low birth weight among babies exposed in utero to topiramate and to some extent, zonisamide.[iv]

Valproic acid has the highest risk for MCMs of all anticonvulsants, between 9 and 10% and is contraindicated in pregnancy except in extenuating circumstances (i.e., the seizures can only be controlled on this drug). Adverse neurocognitive effects of valproic acid have also been identified in one-third of cases within a cohort of children exposed to anticonvulsants and followed since birth.[v] Other anticonvulsants studied in this cohort did not pose increased neurocognitive risk compared to the unexposed control group. Valproic acid is controversial for use in young women of childbearing age in general, especially for alternative indications such as migraine and bipolar disorder due to these risks.

Most other anticonvulsants are considered to be "intermediate" or unknown risk, in which teratogenic risk (between 0 and 4% risk of MCMs) is balanced against the number of cases documented in the North American AED Pregnancy Registry[vi] and many other international registries. Most anticonvulsants - and most medications, for that matter - are listed as Category C for use in pregnancy, associated with some evidence of risk in animals but not enough human data to support an alternative category. Important exceptions to this rule are valproic acid, topiramate and phenobarbital, all of which are listed as Category D (clear evidence of risk to human fetuses) in pregnancy.

Folic acid may help offset risk in pregnant women by protecting specifically against neural tube defects, which are among the most severe of these birth defects. However, there is no consensus on the appropriate dose of folic acid.[vii] Experts recommend between 0.4mg and 10mg per day. Common doses in the United States include between 1 and 5mg/day, and agreement on the proper dose is typically reached through discussion among the patient, the neurologist, and the obstetrician.

Finally, a pre-pregnancy baseline drug level should be checked if the opportunity arises, preferably on a yearly basis. In a seizure-free individual, the pre-pregnancy baseline provides a point of comparison in order to keep the patient seizure-free during pregnancy.[viii]

What are the risks of having a seizure during pregnancy? Should she remain on lamotrigine throughout the pregnancy?

The risks associated with seizures in pregnancy are difficult to quantify but in part relate to trauma resulting from a seizure – this can lead to placental abruption or even miscarriage. Other risks include acidosis, reductions in uterine blood flow and associated hypoxia. It is generally accepted among neurologists and obstetricians that preventing seizures in pregnancy outweighs the significantly lower risk of teratogenicity of anticonvulsants. A 2009 nationwide, population-based study in Taiwan identified a higher risk of preterm labor and delivery as well as a risk of intrauterine growth restriction (IUGR) and delivery of infants who are small for gestational age (SGA) among women with uncontrolled, frequent seizures in pregnancy.[ix] Therefore, the need

to continue anticonvulsants throughout pregnancy should be emphasized to a woman at risk for such. Epilepsy continues to be an important indirect cause of death for a minority of women. Based on the 2011 report of the United Kingdom Confidential Enquiries into Maternal Deaths, 14 deaths were epilepsy-related, of which 11 (79%) were sudden and unexpected (SUDEP)[x].

A long seizure-free interval might predict a seizure-free pregnancy, and the majority of women find that seizure frequency does not change significantly in pregnancy.[xi] Progesterone and its derivatives can have an anticonvulsant effect on the brain, while in some circumstances, estrogen is felt to promote seizures. During pregnancy, both hormones are steadily on the rise. The response of seizures to pregnancy, therefore, is unpredictable. In this particular patient, tapering her lamotrigine in the past resulted in breakthrough seizures, placing her at higher risk for recurrence.

These issues were discussed with the patient, and she, her neurologist and obstetrician opted to continue the lamotrigine at the current dose and preferred a dose of 4mg/day of folic acid in preparation for pregnancy. A pre-pregnancy lamotrigine level was 3.5 - on the lower end of the therapeutic spectrum (between 3.5-15). A few months later, she learned she was pregnant. An urgently scheduled follow-up appointment was made for her.

What counseling should be provided to a woman with epilepsy who has recently discovered she is pregnant? What are the next steps?

Typically, pregnancy-related issues are emphasized once again in a more urgently scheduled visit - ensuring medication compliance and folic acid supplementation. All seizures and auras should be reported to the neurologist. A first-trimester drug level should be checked to ensure stability compared to the pre-pregnancy baseline.

What physiological factors contribute to alteration of anticonvulsant levels in pregnancy? And what is the clinical relevance?

Anticonvulsant levels can plummet during pregnancy due to physiologic alterations that occur from trimester to trimester. This is due to several discrete pregnancy-related physiological factors: an increase in maternal circulatory volume leading to reduced blood concentrations; an increase in the glomerular filtration rate leading to more rapid clearance of the drugs; and the increase in hepatically synthesized proteins altering concentrations of protein-bound drugs as well as metabolic pathways that are influenced by hormones. Nausea and vomiting in pregnant women also contributes to poor absorption of anticonvulsants.

Lamotrigine is extensively metabolized through glucuronidation - a process that is enhanced by sex hormones. More commonly than not, lamotrigine levels drop by up to 50% within the first trimester of pregnancy, with this process beginning before a woman knows she is pregnant, and leaving her less protected from seizures. Therefore, it is possible that pregnancy may present as a cluster of breakthrough seizures. Fortunately, this is the exception rather than the rule! Even the levels of drugs with low protein binding and high renal clearance (rather than hepatic metabolism), like levetiracetam, can drop during pregnancy due to the increased glomerular filtration rate. Because the complex interaction of pharmacology with pregnancy-related

physiology is complicated, a good rule of thumb is to check at least once level per trimester and in the last month of pregnancy.[xii] If the level drops, then an appropriate increase in dose and "re-check" of the level is advised. Women should be counseled that it is more common than not to end up on a higher dose of anticonvulsant during pregnancy than they had been taking previously, because of these factors. After delivery, physiologic and metabolic changes return to the pre-pregnant state at different speeds. Glucuronidation, for example, normalizes within two weeks, and therefore for drugs like lamotrigine, a more rapid taper of the drug to slightly higher than the pre-pregnancy dose over this period is advised.[xiii] It is preferable to be proactive with medication adjustments in response to changing levels in a pregnant woman rather than reacting to seizures and auras, but levels may be prohibited by cost or not be readily available in all institutions. In these cases, clinicians should consider drugs that are more stable from trimester to trimester, drugs with a low toxicity profile even at higher levels (like levetiracetam), or more frequent visits to screen for clinical seizures, auras and signs of toxicity among patients.

Lamotrigine levels throughout the pregnancy ranged from 2.7 to 4.6. She felt well until 29 weeks gestation, when in the context of work stress, sleep deprivation with insomnia, she felt "spacy." She could not tell if she was having true absence seizures. The pros and cons of a medication increase were reviewed, and she decided to make no changes and wait a little longer. Within 6 weeks, she had several recurrent absence seizures and the medication was increased to 400mg/day, which resolved the symptoms. She also took time off work to relieve stress and promote improved sleep – two major seizure triggers. She was seen again at 37 weeks – the final neurology visit before delivery.

What are the next steps?

Her lamotrigine level was checked the same day as the visit. However, because laboratory tests for second generation anticonvulsant levels can take up to several weeks to return, based on location, any breakthrough seizures or auras should prompt an empiric increase in dosage rather than waiting for labs to return. Counseling on adequate sleep is also crucial, as sleep deprivation is a seizure trigger. It is noteworthy that sleep architecture becomes disrupted later in pregnancy, with pregnant women commonly experiencing insomnia and reporting less deep sleep.[xiv]

What peripartum seizure-related issues are important to discuss? Can the patient delivery vaginally (can she push)?

A history of epilepsy in the mother should not influence the mode of delivery. Although caesarean section rate has been higher in women with epilepsy, among other chronic diseases, there is little basis for this clinical trend. Epilepsy is *not* an indication for caesarean section, and there is no evidence that vaginal delivery would increase the risk of seizures for patients.

Labor and delivery for this patient were uneventful, and she delivered a healthy baby girl at full term. During the hospitalization, clinical questions were raised about the emergency treatment of seizures, and also about her ability to breastfeed.

What is the emergency treatment of seizures in pregnancy or the peripartum period, should they occur?

Seizures around the time of labor and delivery are rare, but when they occur, are an emergency. Patients are typically turned on their side to avoid aspiration or compromised airway, and treated aggressively with intravenous medications. Treating the seizing mother urgently is most important for both mother and baby. Most commonly used intravenous options are benzodiazepines (lorazepam, for example), and intravenous loads of phenytoin or levetiracetam. Even when "NPO" patients should be encouraged to take their anticonvulsant medications as usual around labor and delivery.

An important distinction should be made between eclamptic seizures, which are a marker of severe, acute but self-limited neurological disease, and epileptic seizures, which are the result of an underlying chronic condition characterized by a tendency towards (unprovoked) seizures. There is no role for magnesium, the mainstay of therapy in eclampsia, in patients with epileptic (non-eclamptic) seizures. The ideal anticonvulsant for eclamptic seizures should magnesium fail to prevent recurrent seizure activity are yet unknown, and the workup of new onset seizure in the peripartum period usually involves neurological consultation when the presentation does not match eclampsia.

What do you tell her about breastfeeding?

Mothers should be counseled that clinical evidence regarding breastfeeding and anticonvulsants is limited. Lamotrigine does cross into breastmilk and there is a theoretical risk of higher levels in babies due to immature glucuronidation. On the other hand, this is a medication to which babies would have been exposed in utero, and the amount in breastmilk is still quite minimal. There are many advantages to breastfeeding, which should be weighed against possible risks.[xv] Other anticonvulsants are excreted to varying degrees in breastmilk – usually inversely related to the degree of protein binding. Levetiracetam, for example, has very low protein binding and can thus be concentrated in breastmilk. However, the medication itself has a favorable side effect profile for infants and therefore no toxicity has been described. Breastfeeding should be reviewed on a case by case basis with patients. Signs of anticonvulsant toxicity in a baby (while very rare) would include excessive drowsiness.

Are there other postpartum concerns?

One concern postpartum is how quickly to taper the medications back to the pre-pregnancy dosage. Medications that are extensively glucuronidated must be tapered within 2 weeks; however, experts have proposed keeping the dose slightly above the pre-pregnancy dose to partially counteract the potential effects of sleep deprivation on seizure threshold. Other medications can be tapered within 1-3 months, but usually depend on the degree to which they were increased during the pregnancy. Some tapering is recommended to prevent postpartum anticonvulsant toxicity, which can lead to vision and balance problems and potentially falls.

Postpartum safety issues include avoiding baths for mom or the baby when alone in the house, to prevent catastrophic submersion. Heights should be avoided whenever possible – including changing tables when the baby is not strapped in. Co-sleeping should be avoided in women with epilepsy. Alternating feeds with a partner to allow for longer blocks of uninterrupted sleep are

also advisable when possible. In case of an aura, the safest place for the baby is on the floor or in a crib, away from sharp or dangerous objects.

Finally, women with epilepsy are at higher risk for depression, anxiety, and other mental health conditions in general. It is unknown whether they are at higher risk for postpartum depression in particular, but they should be screened and treated accordingly.

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