CASE 2: EPILEPSY AND PREGNANCY

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Case 2:
A 19 year-old woman had two witnessed generalized tonic clonic seizures which occurred two weeks apart. She recalls having some brief jerks in her arms sometimes early in the morning after wakening for several years. Her EEG shows generalized spike-wave discharges. Her initial neurologist titrated lamotrigine as her initial therapy to 100 mg BID. She was free of all generalized tonic-clonic convulsions and had very rare myoclonic jerks in the AM, always provoked by modest sleep-deprivation with 6 hours or less of sleep in the preceding night or two. After completing college, she moved to your city. Six years after initiation of lamotrigine, you receive a call from the emergency room that she was brought in after a witnessed generalized tonic-clonic convulsion by her boyfriend. What are the most pertinent questions to consider for her change in seizure status? You assume her care and after gathering information that she had started the oral contraceptive Seasonique one month ago, you adjust her lamotrigine dose accordingly. She comes to her routine follow-up visit 4 years later and informs you that she wants to try to conceive within the next 6 months. What are the key counseling items to review with her and family members, and how does this change your treatment plan?

Discussion:
The initial monotherapy selection of lamotrigine for her probable diagnosis of Juvenile Myoclonic Epilepsy was appropriate, especially in a young woman of child-bearing potential. She had an established history of good efficacy with lamotrigine, although her history confirms that she is sensitive to the effects of sleep-deprivation.

LAMOTRIGINE AND HORMONAL CONTRACEPTIVES
A series of small studies have demonstrated that lamotrigine serum concentrations are approximately 50% lower in the presence of estrogen-containing contraceptives (combined oral contraceptive pills (COCs), vaginal ring, patch), but are likely unchanged in the presence of progestins only (Nexplanon, Depo-provera, mini pill)[1-3]. Wegner, et al. demonstrated that the lamotrigine level reached its new baseline 8.0 days after the start of COCs, but with a large standard deviation of 3.69 days[4]. In addition to the usual questions about seizure provokers (adherence, sleep-deprivation, stress, illness, other interacting medications), when a woman with epilepsy calls to report an unusual worsening of seizure frequency, it is important to ask if an estrogen-containing contraceptive was started and when her last menstrual period (LMP) occurred, and if she could be pregnant. To prevent seizure worsening with initiation of COCs, there are no Class I or II studies to direct a treatment protocol. However, a rational empiric clinical approach is to increase the lamotrigine dose by 50% when an estrogenic compound is begun, check a lamotrigine blood level approximately 10 days later, and adjust further as needed to obtain the previous established ***individualized target concentration (TC)*** for that woman. It is helpful to establish the lamotrigine concentration at which an individual patient is doing well with stable seizure control and without side effects in the event of changes in interacting medications or pregnancy, keeping in mind that over 50% of pregnancies are unplanned.

Conversely, when a woman is well-controlled on lamotrigine and is on an estrogen-contraceptive, her lamotrigine dosage can be lowered when she stops the contraceptive for pregnancy planning. A report from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) confirmed that in addition to the type of AED, dose of the AED at conception also affects rates of MCMs[5]. MCM rates in pregnancies exposed to carbamazepine (CBZ), lamotrigine (LTG), valproate (VPA), and phenobarbital (PB) were analyzed by dose at time of conception (not throughout the first trimester or entire pregnancy). The lowest rates of MCMs occurred with LTG <300mg/day (2.0%; 95% CI 1.19–3.24), and this group was used as the comparator group. Risks of MCMs were higher with VPA and PB at all doses, and with CBZ at >400mg/day. Additionally, an increase in MCM rates was observed with increasing doses for all four AEDs, in support of the concept that the amount of fetal exposure to an AED is important, as well as the type of AED. Therefore, reduction of the dose prior to conception while maintaining seizure control can further reduce the risk of structural teratogenicity. The study design was not able to address any potential effects of dosage changes during pregnancy, but maintaining the individual TC is known to lower the risk for seizure worsening during pregnancy.

Although this case report emphasizes lamotrigine and the available data is the most robust for this AED, these same principles of increased drug clearance with exogenous or endogenous estrogen increases also applies to valproate[6] and likely to oxcarbazepine, given that glucuronidation is a major metabolic pathway for elimination for all three compounds.

SEIZURES DURING PREGNANCY

The effect of pregnancy on seizure frequency is variable. There is a paucity of studies that are able to truly compare seizure frequency to non-pregnant baseline. These studies that a wide range for the percentage of women who have seizure worsening during pregnancy compared to baseline, with most hovering around 20-50% but as wide as 9-75%[7-14]. Factors that seem to increase the risk of seizure worsening during pregnancy include active seizures in the prior 9-12 months, focal-onset seizures, treatment with lamotrigine or oxcarbazepine (OXC) monotherapy or AED polytherapy, and not using therapeutic drug monitoring[14-16].

Generalized tonic-clonic convulsions (GTCC) can cause maternal and fetal hypoxia and acidosis, fetal heart rate decelerations, and have been associated with miscarriages and stillbirths. Nonconvulsive seizures can cause trauma, which can result in ruptured fetal membranes with an increased risk of infection, premature labor, and even fetal death. Additionally, reemergence of seizures in a woman who had previously experienced seizure control can be devastating. More recent reports have highlighted the potentially higher maternal and obstetric risks during pregnancy, although the methods of the studies have not been able to clearly associate seizures as the primary cause. For example, a recent retrospective cohort study report utilizing delivery hospitalization records from the 2007-2011 Nationwide Inpatient Sample reported that women with epilepsy were at higher risk for several adverse outcomes including preeclampsia, preterm labor, stillbirth, increased health care utilization, including an increased risk of cesarean delivery, most with adjusted odds ratios (OR) around 1.5, but with even higher OR of > 2.0 for prolonged length of hospital stay (>6 days) with cesarean deliveries and with vaginal deliveries[17]. Even more striking was the finding that women with epilepsy had a risk of death *during* delivery hospitalization with an adjusted odds ratio [OR] of 11.46 [95% CI, 8.64-15.19]), although to put this in perspective the baseline rate was 6 deaths per 100 000 pregnancies among women without epilepsy and 80 deaths per 100 000 pregnancies for women with epilepsy. The methods of this study did not allow evaluation of key factors, including verification of epilepsy diagnosis, evaluation of seizure frequency, severity or proximity, cause of maternal mortality, and if mortality was more likely to be associated with seizures, AEDs used, or other factors. Authors of a study from Taiwan reported that seizures in mothers with epilepsy during pregnancy were independently associated with approximately a 1.5-fold increased risk for preterm delivery or infants being born small for gestational age[18]. Future prospective studies of well-defined cohorts will help to sort out potential contributing factors to these increased peripartum risks.

AED MANAGEMENT DURING PREGNANCY

Maintaining seizure stability during pregnancy is dependent on maintaining therapeutic concentrations of the baseline AED. The target concentration should be individually determined, ideally in the preconception phase, for each woman according to her epilepsy history and prior seizure control relative to AED concentrations. During pregnancy, management of the AED dosing becomes complex and requires a more intensive approach than during non-pregnant stages. Clearance of most of the AEDs increases during pregnancy, resulting in a decrease in serum concentrations (Table 3)[19,20]. The 2009 AAN/AES Practice Parameter Update concluded the following: Pregnancy probably causes an increase in the clearance and a decrease in the concentration of LTG, PHT, and to a lesser extent CBZ, and possibly decreases the level of LEV and the active OXC metabolite, the monohydroxy derivative[19].

The magnitude of enhanced clearance of LTG during pregnancy exceeds that described for many of the older AEDs, as hepatic glucuronidation is particularly susceptible to activation during pregnancy due to the direct effects of rising sex steroid hormone levels. Pennell et al. reported that both LTG free and total clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (free) in the 3rd trimester[7]. The authors reported that seizure frequency significantly increased when the LTG level decreased to 65% of the preconception individualized target LTG concentration. This finding supports the recommendation to consider monitoring levels of LTG and other AEDs for which clearance increases during pregnancy[19]. More recently, Pirie et al. [16] performed a meta-analysis of six observational studies to compare the effectiveness of two different monitoring strategies of pregnant women with epilepsy on lamotrigine: therapeutic drug monitoring (TDM) or clinical features monitoring (CFM) to adjust the AED dose. The rate of seizure deterioration was 0.30 (95% CI

0.21–0.41) in women monitored by TDM compared to 0.73 (95% CI 0.56–0.86) in those receiving CFM alone. The authors concluded that observational data suggests that monitoring of AED levels in pregnancy reduces seizure deterioration, although given that the studies were small and with potential sources of bias, further research is needed.

Another argument for TDM is the considerable inter-individual variability in changes in lamotrigine clearance during pregnancy. Polepally and Birnbaum modeled the changes in clearance with gestational age and discovered two subpopulations[21]: 77% of the women had a rapid increase in clearance, with a 10-fold higher rate than 23% of women that had an increase in clearance of only 21% by term. The first group had a 219% increase *above* baseline. The changes in clearance begin immediately with pregnancy and are not independent of weight gain. Therefore, TDM should be begin early during pregnancy, and women should be encouraged to contact their neurologists as soon as they discover they are pregnant.

AEDs other than lamotrigine: Although the most has been studied and written about lamotrigine, similar principles apply to the other AEDs. In addition to accelerated glucuronidation during pregnancy, the cytochrome-P450 enzymes are also up-regulated during pregnancy, maternal albumin decreases leading to altered free fraction of highly-bound AEDs and increased elimination, and renal blood flow increases to 2-3 fold of baseline. Therefore, most AEDs have altered clearance during pregnancy (see Table). In fact, a retrospective study by Reisinger, et al. [13] reported that the percentage of patients with seizure increase during pregnancy were as follows for each of the AEDs: lamotrigine monotherapy (38%), levetiractetam (47%), other monotherapies (20%), and polytherapy (50%). Importantly, seizures worsened significantly during the 2nd trimester when the AED serum concentrations declined to ***≤65%*** of preconception baseline for all AEDs studied.

POSTPARTUM CARE AND BREASTFEEDING

Prior to the delivery, the peripartum plan should be discussed with the patient and family members and shared with other providers. Although AED clearance returns to non-pregnant rates, the length of time over which this occurs varies with the routes of elimination, although there are no definitive studies to map out these time courses. In general, the cytochrome P450 metabolic rates return to non-pregnant baseline over 2-3 months, whereas the glucuronidation pathway and renal clearance return to baseline over 2-3 weeks. Early reports of LTG use in pregnancy noted post-partum symptomatic toxicity. Pennell et al.[7] examined the effectiveness of using an empiric postpartum taper schedule for LTG, with steady decreases in dosing at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep-deprivation. Patients were assessed for symptoms of LTG toxicity. Non-adherence to the standard taper schedule was associated with significantly higher risk of experiencing postpartum toxicity. The usefulness of TDM is limited in the postpartum state with medications that have rapid changes in clearance rates, since steady-state is never really obtained.

One study reported that the highest period for seizure exacerbation was in the three days peripartum (one day prior to delivery through one day after delivery), and the risk was especially high for women who had seizures in the pre-pregnancy month[14]. Since sleep-deprivation and stress remain high for at least a few months after delivery, it is helpful to consider this time as higher seizure risk even when a patient has been seizure-free for an extended period of time. Safety issues should be addressed including extra precautions for all seizure types for the patient. For example, if a woman has myoclonic jerks, use of a harness when carrying the newborn is helpful. Co-sleeping should be discouraged. Water safety for mother and baby should be discussed, as well as a temporary pause on driving privileges should be considered.

Most infants of women with epilepsy can successfully breastfeed without complications. The concentrations of the different AEDs in breast milk are less than those in maternal serum for many of the AEDs, and when infant's serum concentrations have been measured, they are significantly less than maternal paired serum concentrations[19,22,23]. The benefits of breast-feeding are believed to outweigh the small risk of adverse effects of AEDs. Findings from the NEAD cohort actually demonstrated a benefit to breastfeeding; adjusted IQ was actually higher by 4 points for children who were breastfed vs. those who were not[24,25]. The benefits of breastfeeding should be presented in the context of the adverse effects of sleep-deprivation on seizure control, especially if a woman has a type of epilepsy syndrome or a history that demonstrates sleep sensitivity. One useful strategy is to suggest use of a combination of breastfeeding with bottle feeding (of formula or pumped breastmilk) to allow the mother to get at least one longer stretch of sleep each night.

Salient Points for Consideration in this Case:

1. Aim for seizure freedom prior to pregnancy with use of monotherapy with an AED that has a favorable teratogenic profile.
2. Establish the patient's individual target concentration at which seizures are optimally controlled and without side effects.
3. Reassess if the patient is likely to get the same results with an even lower dose, especially if the dose is higher than the lowest-risk ranges reported by EURAP[5].
4. If a woman of childbearing age reports seizure worsening, consider if she could be pregnant or if she started an estrogen-containing contraceptive if she is on lamotrigine, oxcarbazepine, or valproate.
5. If a woman stops an estrogen-containing contraceptive in preparation for pregnancy, and she is on lamotrigine, oxcarbazepine or valproate, this is an ideal opportunity to lower her daily dose to generate a serum level within her individualized target concentration.
6. Therapeutic drug monitoring has been shown to be beneficial for many AEDs during pregnancy, with monthly serum levels, adjusted for seizures or side effects.
7. Ask women with epilepsy of childbearing age to contact her neurologist as soon as she knows she is pregnant, because her pregnancy may change the level of her AED and levels may need to be monitored to adjust dose to avoid seizures.
8. Peripartum is a vulnerable period for seizure worsening.
9. Postpartum AED dosage taper schedules should be provided to the patient.
10. Breastfeeding when a woman is on AEDs has the same benefits to the mother and child, but may need to be modified to avoid extreme sleep-deprivation.

Table. Alterations of Antiepileptic Drug Clearance and/or Concentrations During Pregnancy: summary of Class I, II, and III studies[19,22]

Antiepileptic Drug	Reported Increases in Clearance	Reported Decreases in Total Concentrations	Reported Changes in Free AED or Metabolites
Phenytoin	19 -150%	60-70%	Free phenytoin clearance increased in trimester 3 by 25%; free phenytoin concentration decreased by 16-40% in trimester 3
Carbamazepine	-11 to +27%	0%–12%	No change
Phenobarbital	60%	55%	Decrease in free phenobarbital concentration by 50%
Primidone	Inconsistent	Inconsistent	Decrease in derived PB concentrations, with lower PB/PRM ratios
Valproic acid	Increased by trimesters 2 and 3		No change in clearance of free VPA. Free fraction increased by trimesters 2 and 3
Ethosuximide	Inconsistent	Inconsistent	
Lamotrigine	65% - 230%, substantial interindividual variability		89% increase in clearance of free lamotrigine
Oxcarbazepine		Monohydroxy derivative & active moiety decreased by 36-61%	
Levetiracetam	243%	60% by trimester 3	

REFERENCES

1. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. Epilepsia 2005;46:1414-7.
2. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001;47:151-4.
3. Sabers A, Ohman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003;61:570-1.
4. Wegner I, Edelbroek PM, Bulk S, Lindhout D. Lamotrigine kinetics within the menstrual cycle, after menopause, and with oral contraceptives. Neurology 2009;73:1388-93.
5. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10:609-17.
6. Herzog AG, Blum AS, Farina EL, et al. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology 2009;72:911-4.
7. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 2008;70:2130-6.
8. Petrenaite V, Sabers A, Hansen-Schwartz J. Individual changes in lamotrigine plasma concentrations during pregnancy. Epilepsy Res 2005;65:185-8.
9. Harden C.L. PPB, Koppel B.S., Hovinga C.A., Gidal B., Meador K.J., Hopp J., Ting T.Y., Hauser W.A., Thurman D., Kaplan P.W., Robinson J.N., French J.A., Wiebe S., Wilner A. N., Vasquez B., Holmes L., Krumholz A., Finnell R., Shafer P.O. . Practice Parameter Update: Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding. Neurology 2009;submitted.
10. Sabers A, Petrenaite V. Seizure frequency in pregnant women treated with lamotrigine monotherapy. Epilepsia 2009;50:2163-6.
11. Harden CL, Hopp J, Ting TY, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009;50:1229-36.
12. Wegner I, Edelbroek P, de Haan GJ, Lindhout D, Sander JW. Drug monitoring of lamotrigine and oxcarbazepine combination during pregnancy. Epilepsia 2010;51:2500-2.
13. Reisinger TL, Newman M, Loring DW, Pennell PB, Meador KJ. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. Epilepsy Behav 2013;29:13-8.
14. Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia 2012;53:e85-8.
15. Battino D, Tomson T, Bonizzoni E, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54:1621-7.
16. Pirie DA, Al Wattar BH, Pirie AM, et al. Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2014;172:26-31.
17. MacDonald SC, Bateman BT, McElrath TF, Hernandez-Diaz S. Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States. JAMA neurology 2015;72:981-8.

18. Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009;66:979-84.
19. Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:142-9.
20. Pennell PB, Hovinga CA. Antiepileptic drug therapy in pregnancy I: gestation-induced effects on AED pharmacokinetics. Int Rev Neurobiol 2008;83:227-40.
21. Polepally AR, Pennell PB, Brundage RC, et al. Model-Based Lamotrigine Clearance Changes during Pregnancy: Clinical Implication. Ann Clin Transl Neurol 2014;1:99-106.
22. Hovinga CA, Pennell PB. Antiepileptic drug therapy in pregnancy II: fetal and neonatal exposure. Int Rev Neurobiol 2008;83:241-58.
23. Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. Pediatrics 2008;122:e223-31.
24. Meador KJ, Baker GA, Browning N, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 2010;75:1954-60.
25. Meador KJ, Baker GA, Browning N, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr 2014;168:729-36.