Managing Epilepsy in Women: Special Considerations

How high is your knowledge quotient on special considerations in the treatment of women with epilepsy? In a presentation on managing epilepsy in special populations, Trevor J. Resnick, MD, director of the Division of Pediatric Neurology at the University of Miami, cited survey results published back in November 2000 in The Journal of Women's Health and Gender-Based Medicine, which illustrated that only 5% of the 3535 practitioners surveyed answered two thirds of the questions correctly. "Almost a quarter didn't know that there was a relationship between seizures and hormonal cycles. Over 80% didn't know that women with epilepsy have lower fertility rates. Two thirds didn't know that women are at a higher risk for osteoporosis and osteopenia. Three quarters didn't know which antiepileptic drugs-and this is very important-interacted and which did not interact with oral contraceptives," stated Resnick in his presentation at a symposium on advances in neurology held recently in New York City.

SEIZURES AND CYCLING In treating women, think "catamenial epilepsy," Resnick recommended. Epileptic patterns correspond with menstrual cycles in up to 50% of affected women. Seizures will likely be more frequent as mid-cycle approaches and estrogen levels build and less frequent during the luteal phase, when estrogen levels fall and progesterone levels increase. "Because of high estrogen, which is a proconvulsant, there is going to be greater vulnerability to seizures just before and during flow and just prior to ovulation. Often there ends up being 2 cycles during the whole cycle where seizures may increase," he said. Taking this into account will enhance seizure control, which, of course, is the goal. Although it may remain an ideal, the practitioner should not desist in striving for 100% seizure control, said Resnick, noting that epilepsy in the general population is associated with significant mortality due to status epileptics (incidence, 10%), suicide (incidence, 7% to 22%), and a phenomenon called "sudden unexplained death in an epileptic patient" (incidence, 8% to 17%, with significantly higher rates seen in poorly controlled disease). Of importance is choosing an antiepileptic drug (AED) that does not interfere with oral contraceptives. "Many antiepileptic drugs are very powerful enzyme inducers. Because oral contraceptives and [older] antiepileptic drugs are metabolized through the same enzyme system in the liver, you are going to render women less protected if they are on [these] antiepileptic drugs and oral contraceptives at the same time," cautioned Resnick. Carbamazepine, phenytoin (Dilantin, Park-Davis), and phenobarbital in particular interfere with the efficacy of oral contraceptives, although newer agents, such as gabapentin (Neurontin, Park-Davis) and levetiracetam (Keppra, Elan Pharmaceuticals/UCB Pharma) do not because they are not metabolized in the liver. As far as appropriate AED selection for women and others with epilepsy is concerned, Resnick made a point to state that older and newer AEDs have been shown to have equal efficacy. The advantage of the newer agents is that besides being less likely to interfere with the effect of oral contraceptives, they have a better side-effect profile and are better tolerated in general than older drugs. "If you have a choice, first of all, use an AED that does not affect the oral contraceptive metabolism, or if you're going to have to do that, use an oral contraceptive that contains at least 50 microg/d of estradiol or mestranol, and always encourage patients to use alternatives or supplementary methods, as well," he recommended. He noted that seizures may become less frequent after menopause, when the estrogen/progesterone ratio shifts, although by the same token,
seizures may increase in women receiving hormone replacement therapy (HRT)—a tradeoff that the practitioner should discuss with the patient considering HRT. FERTILITY AND PREGNANCY "We know that fertility is affected by epilepsy and epileptic drugs," said Resnick. He noted that the fertility rate among women with epilepsy is about 40% that of age-matched siblings. Causes of infertility in this patient group are multidimensional, though. Women with epilepsy are more prone to anovulatory menstrual cycles, menstrual disorders, and early miscarriages than are healthy women. Marriage rates also are lower. Special considerations need to be taken for women with epilepsy who want to become pregnant or who are pregnant. "Because of hormonal issues, the frequency of seizures may increase during pregnancy," Resnick reminded the audience. The risk of teratogenicity also is a major concern. Resnick noted, however, that some patients may have a genetic predisposition that makes them more vulnerable than others to AED-induced teratogenic effects. Therapeutic choices must be carefully considered. "Most of the older drugs at least double the risk of birth defects from 2% - 3% to 4% - 6%. Specifically, neural tube defects are associated with valproic acid and, to a lesser extent, carbamazepine," said Resnick, who added that pretreating patients with folic acid at dosages in excess of 0.4 mg/d will help reduce the risk of neural tube defects. In all, he noted that a growing body of evidence suggests that the newer AEDs may be safer for use in pregnant patients and in patients planning to become pregnant than are the older AEDs. To reduce the risk of birth defects and maintain seizure control, aim to optimize therapy before pregnancy occurs. "You don't want to be trying to achieve decent seizure control during the first trimester," stressed Resnick. The aim is to use the lowest possible dose of an AED, which needs to be defined long before pregnancy occurs. Resnick also recommended antiepileptic monotherapy and high-dose folic acid supplementation (Table 1).

POLYCYSTIC OVARIAN SYNDROME The overall rate of polycystic ovarian syndrome (PCOS) in premenopausal women is estimated to be about 6.6%.8 PCOS is significantly more common, however, among women with epilepsy. Resnick cited an Italian study led by Leonilda Bilo, MD, PhD,9 in which reproductive endocrine disorders were diagnosed in 16 (32%) of 50 women with epilepsy. The most common diagnosis was PCOS, accounting for 81% of the diagnoses. PCOS is characterized by high levels of androgen. The ratio of leuteinizing hormone to follicle-stimulating hormone may be more than doubled. "Because of this high-androgen state, women with polycystic ovarian syndrome have a much higher incidence of diabetes, cardiovascular disease, and endometrial cancer. You're not just dealing with the epilepsy; you're dealing with long-term consequences that have additional bearing on lifespan and quality of life," remarked Resnick. He added that it is important to distinguish between PCOS and the simple presence of a polycystic ovary (Table 2), the latter being "just a state where there are at least 10 subcapsular follicular cysts of a certain size but without any of the other associated features. So, just the fact that an ultrasound may show polycystic ovaries does not necessarily mean that [the patient] has polycystic ovarian syndrome," said Resnick. OSTEOPOROSIS Although there doesn't seem to be a strong association between PCOS and AED use, low bone density in patients, regardless of age or sex, has been linked to such use. "Everyone knows that there is a 4-fold increase in the risk of femoral neck fractures in patients with epilepsy compared with age-matched controls," noted Resnick. He said that enzyme-inducing AEDs play a major role in the development of this complication. "There is a lack of knowledge concerning screening, prevention, and treatment of bone disease in women with epilepsy," Resnick said, citing findings from the aforementioned survey in The Journal of Women's Health and Gender-Based Medicine.1 Definitive preventive strategies have yet to be defined.1 HRT may help prevent bone loss, but it also may have a negative impact on seizure control.10 It is an area in need of further investigation, noted Resnick, who recommended that patients be counseled early about exercise and diet, smoking habits, and vitamin D and calcium supplementation. References 1. Morrell MJ, Sarto GE, Shafer PO, et al. Health issues for women with epilepsy: a descriptive survey to assess knowledge and awareness among healthcare providers. J Womens Health Gend Based Med. 2000;9:959-965. 2. Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. Epilepsia. 1997;38:1082-1088. 3. Shorvon SD. The epidemiology and treatment of chronic and refractory epilepsy. Epilepsia. 1996;37(suppl 2):S1-S3. 4. Nashef L, Fish DR, Garner S, et al. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. Epilepsia. 1995;36:1187-1194. 5. Cramer JA Jones EE. Reproductive function in epilepsy. Epilepsia. 1991;32(suppl 6):S19-S26. 6. Yerby MS. Quality of life, epilepsy advances, and the evolving role of anticonvulsants in women with epilepsy. Neurology. 2000;55(suppl 1):S21-S31. 7. Cantrell DC, Cunningham FG. In: Cunningham FG, Gant NF, Leveno KJ, et al, eds. William Obstetrics, Supplement No. 8. Norwalk, Conn: Appleton & Lange; 1998:1-14. 8. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004;89:2745-2749. 9. Bilo L, Meo R, Valentino R, et al. Characterization of
reproductive endocrine disorders in women with epilepsy. J Clin Endocrinol Metab. 2001;86:2950-2956. 10. Harden CL, Pulver MC, Ravdin L, Jacobs AR. The effect of menopause and perimenopause on the course of epilepsy. Epilepsia. 1999;40:1402-1407. --- Table 1 - Strategies to reduce risk of birth defects - Aim for monotherapy - Optimize antiepileptic therapy before pregnancy occurs - Use lowest possible effective dose of an antiepileptic drug - Use folic acid (at least 0.4 mg/d) supplementation throughout pregnancy - Perform prenatal diagnostic testing at 16 to 18 weeks (ie, maternal serum a-fetoprotein testing and anatomic ultrasonography) --- Table 2 - Polycystic ovary syndrome (PCOS) vs presence of polycystic ovary PCOS Presence of follicular cysts (greater than or equal to 10 subcapsular cysts measuring 2 - 8 mm in diameter and arranged around or within thickened ovarian stroma) Ovulatory dysfunction Clinical evidence of hyperandrogenism and/or hyperandrogenemia Diagnostically evident absence of adrenal or thyroid disease, including Cushing syndrome, cancer, and congenital adrenal hyperplasia Polycystic ovary Presence of follicular cysts (greater than or equal to 10 subcapsular cysts measuring 2 - 8 mm in diameter and arranged around or within thickened ovarian stroma) Above by itself, not diagnostic of PCOS


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