Women with Epilepsy

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I. Contraception
   a. Why important for women with epilepsy?
      i. Average woman in the US will spend 30 years preventing pregnancy and five years seeking pregnancy and then bearing children
      ii. Effective contraception is necessary to optimize pregnancy outcomes.
   b. Types of contraception:
      i. Barrier methods: condoms (male, female), diaphragm, cervical cap, spermicides (VCF, foam, gel, sponge)
      ii. Hormonal methods: combined hormones (pill, patch, vaginal ring), progestin only methods (pill, implant, Depo-Provera IM injection)
      iii. Intrauterine device (IUD): hormonal or copper (hormonal or copper)
      iv. Sterilization: vasectomy, tubal ligation
   c. Bidirectional interactions occur between some antiepileptic drugs (AEDs) and hormonal contraception: (Davis A, Pack A, Dennis A. Chapter 8: Contraception for women with epilepsy. In: Allen R, Cwiak C, eds. Contraception for the Medically Challenging Patient. New York, NY: Springer; 2014: 135-146)
      i. Lamotrigine is eliminated by conjugation with glucuronic acid, a reaction catalyzed by the uridine 5'-diphosphate (UDP)-glucuronosyltransfereases (UGTs). Estrogens are also metabolized by glucuronidation. The combination of lamotrigine and estrogen containing hormonal contraception increases the metabolism of lamotrigine, likely through induction of the glucuronidation pathway, resulting in decreased serum lamotrigine concentrations and potential increased seizure frequency. Lamotrigine levels do not change when taken in combination with progestin-only agents. When prescribed estrogen containing contraception, adjustments in lamotrigine dosing will need to be made to ensure stable lamotrigine concentrations.
      ii. Lamotrigine may reduce levonorgestrel (progestin) concentrations of combined hormonal contraception. Levonorgestrel levels in one cross over study of 16 healthy women given lamotrigine decreased by 12% but the concentration of ethinyl estradiol did not change. Although progestins

are more important for contraceptive effectiveness, findings suggested that these women likely did not ovulate and were therefore not at risk for getting pregnant. Further research is needed to clarify if, and how, this commonly used drug impacts contraceptive effectiveness.

iii. AEDs that induce cytochrome P450 enzymes cause enhanced metabolism of contraceptive steroids resulting in decreased efficacy. Combined oral contraceptives have received the most study with co-administration of AEDs; minimal published data examine patches or rings. Carbamazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide all induce the cytochrome P450 enzyme system. For women with epilepsy prescribed these cytochrome P450 enzyme inducing AEDs and a combined hormonal method of contraception, dual method use (eg hormonal therapy plus barrier method) use is encouraged and preparations with a minimum of 35 micrograms of ethinyl estradiol are recommended.

iv. Although topiramate is considered an enzyme inducing AED, particularly at higher doses, it has selective effects on components of combined hormonal contraception. In one small study (n=12) topiramate administration (dose range 100 to 400 mgs) when given in combination with combined hormonal contraception affected ethinyl estradiol but not norethindrone (progesterone) concentrations. This is relevant because progestins are more important for contraceptive effectiveness. Topiramate therefore likely does not result in decreased effectiveness of combined hormonal contraception. (Rosenfeld et al. Epilepsia 1997;38(3):317-323.)

d. Hormonal IUDs likely do not affect seizure control or AED concentrations. A study of 20 women with epilepsy on stable AED regimens who had the Mirena IUD placed had no significant change in seizure frequency or AED concentrations (Davis et al. Epilepsia 2016;57(11):1843-1848).

II. Pregnancy

a. Birth rates are reported to be lower among WWE. In a Finnish study using national insurance data, birth rates among WWE were 17% lower than in the general population (Viinikainen et al. Neurology 2007;69(22):2107-2108.). Birth rates, however are not a direct indicator of fertility as some WWE women may choose not to have a child because of AED effects on pregnancy outcomes and population studies often include WWE who have comorbidities and are unlikely to choose to get pregnant. Using more than one AED is a significant factor associated with difficulty conceiving among WWE seeking pregnancy (Sukumaran et al. Neurology 2010; 75(15):1351-1355.).

b. Preconceptual counseling is important to optimize pregnancy outcomes. Studies find that at least 50% of pregnancies among women with epilepsy are unplanned. (Davis et al. Contraception 2008;77(6):405-409) and Herzog et al. Neurology 2017;88(8):728-733.)
c. Folic acid supplementation
    i. In the general population, folic acid supplementation during pregnancy has been associated with a significant risk reduction of occurrence of congenital malformations.
    ii. AAN and AES recommend that reproductive aged women with epilepsy receive at least 400 mcg per day. (Harden et al. Epilepsia 2009;50(5):1247-1255. Harden et al. Neurology 2009;73(2):142-149.)
        1. Women with epilepsy taking valproate should take higher doses as it is associated with higher risk of neural tube defects and adverse cognitive outcomes. ((Jentnik et al. NEJM 2010;362:2185-2193.)
        2. Carbamazepine is also associated with a higher risk of major congenital malformations and women with epilepsy prescribed this medication should also take higher daily folic acid doses. (Jentnik et al. BMJ 2010;341:6582.)
    iii. Published studies however, do not show a benefit of folic acid supplementation in reducing risk of major congenital malformations. (Ban et al. PLoS One 2015;10(7): e0131130.)
    iv. A prospective study of neurodevelopmental outcomes in children exposed to AEDs in utero did however, show that folic acid supplementation resulted in better cognitive outcomes. (Meador et al. Brain 2011;134:396-404.)
    v. Another report found that folic acid supplementation before pregnancy reduced the risk of spontaneous abortion in women with epilepsy. (Pittschieler et al. J Neurol 2008;255(12):1926-1931).
d. Although the majority of WWE have normal healthy babies there is an increased risk of major congenital malformations when compared to the general population. A major congenital malformation is defined as a structural abnormality with surgical, medical or cosmetic importance:
    i. Ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, aortic valve stenosis, hypoplasia of mitral valve
    ii. Cleft lip and cleft palate
    iii. Penile hypospadias, imperforate anus, spina bifida
    iv. Talipes equinovarus (club foot), calcaneovalgus (flexible flat foot) terminal transverse limb defects, hip dysplasia, inguinal hernia

e. AEDs in monotherapy are associated with variable rates of major congenital malformations. Current reported malformations rates are obtained from multiple registries. Methodology is different among registries and therefore reported malformation rates cannot be directly compared. Table i and ii below detail reported major congenital malformation rates from different registers of AEDs below as monotherapy. Number of exposures are in parentheses. Tables iii and iv detail relative risks comparing risk of major congenital malformations between AED exposed children to children born to women without epilepsy (table iii) and to children born to women with untreated epilepsy from Cochrane Database analyses. Overall risk of major congenital malformations is higher for children exposed to AEDs in utero with the highest risk associated with valproate. (Weston et al. Cochrane Database Sys Rev 2016)

i. Reported major congenital malformation rates: Older AEDs (pre-1990)

Register	AED			
	Valproate	Carbamazepine	Phenytoin	Phenobarbital
Swedish	9.7% (268)	4.0% (703)	---	---
Finnish	10.7% (263)	3.5% (805)	---	---
UK	6.7% (1290)	2.6% (1718)	---	---
North American	9.3% (323)	3.0% (1033)	2.9% (416)	5.5% (199)
Australian	13.1% (374)	6.3% (301)	2.9% (35)	---

ii. Reported major congenital malformation rates: Newer AEDs (post-1990)

Register	AED		
	Lamotrigine	Levetiracetam	Topiramate
UK	2.3% (2198)	0.7% (304)	9.0% (203)
North American	2.0% (1562)	2.4% (450)	4.2% (359)
Australian	5.2% (231)	0 (22)	3.2% (31)

iii. Cochrane Database analysis: AED exposed children compared to children born to women without epilepsy.

AED	Sample Size	RR (95% CI)
Carbamazepine	1367 vs 2146	2.01 (1.2 to 3.36)
Phenobarbital	346 vs 1591	2.84 (1.57 to 5.13)
Phenytoin	477 vs 987	2.38 (1.12 to 5.03)
Topiramate	359 vs 442	3.69 (1.36 to 10.07)
Valproate	467 vs 1936	5.69 (3.33 to 9.73)

iv. Cochrane Database analysis: AED exposed children compared to children born to women with untreated epilepsy.

AED	Sample Size	RR (95% CI)
Carbamazepine	3058 vs 1287	1.50 (1.03 to 2.19)
Phenytoin	640 vs 1256	2.40 (1.42 to 4.08)
Valproate	1923 vs 1259	3 (2.16 to 4.54)

f. Valproate and carbamazepine are associated with an increased risk of neural tube defects.
   i. Case control study found odd ratio of 12.7 with valproate exposure (Jentnik et al. NEJM 2010;362:2185-2193.).
   ii. Case control study found odds ratio of 2.6 with carbamazepine exposure (Jentnik et al. BMJ 2010;341:6582.).

g. Higher AED doses are associated with increased risk of major congenital malformations. Understand effect of higher AED doses on MCM rates
   i. In the European epilepsy and pregnancy registry study an increase in malformation rate with increasing dose at the time of conception was recorded for all AEDs studied (carbamazepine, lamotrigine, valproic acid, phenobarbital). (Tomson et al. Lancet Neurol 2011;10(7):609-617.).

h. Most women maintain good seizure control during pregnancy.
   i. Seizure control for at least nine months prior to pregnancy is usually associated with a high rate (84-92%) of remaining seizure free. (Harden et al. Neurology 2009;73(2):142-149.)
   ii. Reasons for increased seizure frequency during pregnancy

1. Noncompliance: prospective observational study of 86 women with epilepsy seeking pregnancy found a 75% compliance rate (Ernst et al. Epilepsia 2016;57(12):2039-2044.).
2. Pharmacokinetic changes
3. Sleep deprivation
4. Medication changes

i. Generalized convulsive seizures during pregnancy results in multiple potential adverse effects. Unknown risk of other seizure types. Potential adverse effects of generalized convulsive seizures:
   i. Increased pressure in pregnant uterus.
   ii. Trauma if woman falls during seizure.
   iii. Fetal bradycardia
   iv. Status epilepticus can result in intrauterine death
   v. Decreased verbal IQ in association with >5 generalized convulsive seizures. (Adab et al. J Neurol Neurosurg Psychiatry 2004;75:1575-1583.)

j. Children exposed to valproate in utero are at increased risk for lower IQ and autistic spectrum disorder.
   i. NEAD study (Neurodevelopmental Effects of Antiepileptic Drugs): Pregnant women taking carbamazepine, lamotrigine, phenytoin, and valproate were enrolled and their children were followed prospectively. After controlling for maternal IQ, AED dose, gestational age, and folate supplementation, IQ at age six was lower in valproate exposed children. (Meador et al. Lancet Neurol;12(3):244-252.)
   ii. Reported 6-8% prevalence of autistic spectrum disorders in children exposed to valproate in utero compared to background risk of 1-2%. (Bromley. Reprod Toxicol 2016;64:203-210)

k. All AED concentrations need to be followed throughout pregnancy as they will decrease.
   i. Check total and free
   ii. Lamotrigine concentrations need to be checked at least monthly as the concentrations decrease because of estrogen mediated accelerated glucuronidation. (Tomson et al. 2013;54(3):405-414).

l. Breastfeeding is recommended for women with epilepsy taking AEDs.
   i. Concentration of AED in breast milk is inversely related to percentage of protein binding.

ii. Individual breast milk plasma ratios

AED	Ratio
Carbamazepine	0.69
Lamotrigine	0.6
Phenobarbital	0.4-0.6
Phenytoin	0.45
Primidone	0.72
Valproate	0.42

iii. No adverse cognitive effects of breastfeeding are reported among children whose mother have epilepsy and take AEDs. (Veiby et al. JAMA Neurol 2013;70:1367-1744. and Meador et al. JAMA Pediatr 2014;168:729-736.)

III. Catamenial Epilepsy
   a. Definition: Seizure exacerbation related to menstrual cycle.
   b. Three patterns of catamenial epilepsy (Herzog et al. Epilepsia 1997;38(10):1082-1088.
      i. Catamenial pattern 1 (C1): perimenstrual (days -3 to 3 of menstrual cycle whereby day 1 is first day of menstrual cycle)
      ii. Catamenial pattern 2 (C2): periovulatory during normal ovulatory cycles (days 10 to -13)
      iii. Catamenial pattern 3 (C3): luteal phase in adequate luteal phase cycles (days 10 to 3)
   c. Mechanisms to explain catamenial epilepsy
      i. Progesterone: antiepileptic properties (Bäckström et al. Acta Neurol Scand 1984;69:240-248. Reddy et al. Neuropharmacology 2010;59:573-581; Reddy and Mohan. J Neurosci 2011;31:650-658; Reddy and Ramanathan. Epilepsy Behav 2012;25:92-97. Reddy. Front Cell Neurosci 2013;7:1-20; Tauboll et al. Seizure 2015;28:3-11.)
         1. Mediated by conversion to allopregnanolone:
            a. Neurosteroid
            b. Positive allosteric modulator of GABAa conductance
            c. Increases inward chloride current induced by GABA.
         2. Progesterone in rodent models at low doses suppressed rate of development of kindled activity evoked by daily hippocampal stimulation.
         3. Progesterone infusions in women with epilepsy reduced seizure activity.

ii. Estrogen: proconvulsant properties (Logothetis et al. Neurology 1959;9:352-360; Scharfman et al. Ann Neurol 2008;64:687-697; Reddy. Epilepsy Res 2009;85:1-30; Reddy. Front Cell Neurosci 2013;7:1-20; Tauboll et al. Seizure 2015;28:3-11.)
    1. Proconvulsant effects in ovariectomized rats
    2. Epileptic female rats show cyclic increases in epileptiform activity in EEG recordings that coincide with ovarian cycle, likely attributable to estrogens
    3. Estradiol increases production and density of NMDA receptors on dendritic spines of hippocampal CA1 pyramidal neurons and Purkinje neurons: NMDA receptors leads to increased intracellular calcium entry resulting in more excitatory inputs to pyramidal cells
    4. Suppresses GABAergic inhibition of hippocampal neurons
    5. After receiving IV estrogen (Premarin), 11/16 women with epilepsy had increased epileptogenic activity on EEG and 4 experienced seizures

d. Pregnant women with catamenial epilepsy have improved seizure frequency likely secondary to absence of cyclical hormone variations. (Cagnetti et al. Neurology 2014;83(4):339-344.)
e. Treatment strategies for women with catamenial epilepsy
    i. First line of treatment is AED therapy
    ii. Hormonal therapy
    iii. Acetazolamide during vulnerable time
    iv. Benzodiazepines during vulnerable time
    v. Increased AED medication during vulnerable time
f. Progesterone Treatment Trial: A randomized clinical trial (Herzog et al. Neurology 2012;78(24):1959-1966.)
    i. Randomized, double-blind, placebo-controlled, phase III, multicenter, clinical trial compared the efficacy and safety of adjunctive cyclic natural progesterone therapy vs placebo treatment of intractable seizures in 294 subjects randomized 2:1 to progesterone or placebo, stratified by catamenial and noncatamenial status.
    ii. Provided Class III evidence that cyclic progesterone is ineffective in women with intractable partial epilepsy.
    iii. Post hoc analysis identified that a subset of women with higher levels of perimenstrual seizure exacerbation were responsive to progesterone treatment.

IV. Reproductive Health
    a. Reproductive dysfunction is reported among women with epilepsy (Isojärvi et al. N Engl of Med 1993;329:1383-1388; Bauer et al. J Neurol Neurosurg Psychiatry 2002;73:121-125; Harden et al. Neurology 2003;61:451; Löfgren et al. Epilepsy Behav 2007;10:77-83; Hamed. Expert Rev Clin Pharmacol 2015;8:741-750)
        i. Hyposexuality most common abnormality
        ii. Menstrual disorders with ovulatory failure
        iii. Hyperandrogenism and polycystic ovarian syndrome
            1. Valproate can induce androgen synthesis and is associated with increased testosterone
            2. More frequent in women with idiopathic generalized epilepsy syndromes
        iv. Hypothalamic amenorrhea
        v. Premature menopause
        vi. Hyperprolactinemia: High LH and altered LH/FSH ratio

V. Menopause
    a. Increased rates of premature menopause characterized by amenorrhea and ovarian failure have been reported in women with epilepsy. (Harden et al. Neurology 2003;61:451-455.)
    b. Hormone replacement therapy is associated with a dose related increase in seizure frequency in postmenopausal women with epilepsy. (Harden et al. Epilepsia 2006;47(9):1447-1451)

VI. Bone Health
    a. Fracture rates are 2-6-fold increased when compared to the general population. (Annegers et al. Epilepsia. 2004; Cummings et al. N Engl J Med. 1995; Espallargues et al. Osteoporosis Int. 2001; Jetté et al. Jama Neurology 2011; Petty et al. Epilepsia 2010; Scane et al. Osteoporosis Int. 1999; Souverein et al. Epilepsia 2005; Vestergaard et al. Epilepsia 2004)
        i. Factors that increase risk of fracture:
            1. Risk higher with generalized convulsive seizures
            2. Long term effects of AEDs on bone.
                a. Increased risk with longer duration of AED therapy.
            3. Poor coordination secondary to side effects.
            4. Significant mean within-pair differences in tests of static and dynamic balance between AED users and siblings pairs without epilepsy not taking AEDs.
    b. Bone mineral density in persons with epilepsy (Farhat G, et al. Neurology. 2002; Andress DL, et al. Arch Neurol. 2002; Tsukahara H, et al. Pediatr Int. 2002; Guo C, et al. Epilepsia. 2001; Sheth RD, et al. J Pediatr. 1995; Chung S, Ahn C.

Brain Dev. 1994; Ensrud KE, et al. Neurology. 2004; El-Hajj Fuleihan et al. Bone, 2008; Stephen et al, Seizure, 1999)

i. Bone mineral density generally between 10 and 16 percent below controls.
ii. Factors associated with lower bone mineral density
    1. Older age
    2. AED polytherapy
    3. Use of enzyme inducing AEDs
    4. Developmental delay

c. Metabolic bone abnormalities in persons with epilepsy
    i. Lower serum calcium
    ii. Lower serum phosphate
    iii. Higher serum parathyroid hormone
    iv. Lower serum vitamin D metabolites
    v. Increased serum markers of bone formation
    vi. Increased serum and urine markers of bone resorption
d. Mechanisms to explain bone health abnormalities associated with AEDs (Pack AM. Anticonvulsant-related bone disease. In: Marcus R, Feldman D, Dempster D, Luckey M, Cauley J, editors. Osteoporosis. 4th ed. New York: Elsevier; 2013. p. 1225–35.)
    i. Cytochrome P450 enzyme induction leading to accelerated vitamin D metabolism, reduced active vitamin D metabolites, increased parathyroid hormone, increased bone turnover, decreased bone mineral density
    ii. Impaired absorption of calcium
    iii. Vitamin K deficiency
        1. Vitamin K is a cofactor required for carboxylation of Gla proteins (osteocalcin most abundant); Poorly carboxylated osteocalcin associated with decreased BMD and increased fracture risk.
        2. Phenytoin administration decreases serum vitamin K2 and BMD in animal models. Effects reversed with vitamin K2 administration
        3. High dose vitamin K2 increased BMD in a small group of persons with epilepsy
    iv. Direct effects of phenytoin to stimulate bone resorption and subsequent decreased bone mineral density
    v. Impact of genetics (Phaphal et al. Epilepsia 2013;54(2):249-255).
        1. Subjects with B allele of BsmI polymorphism of VDR receptor at increased risk for decreased bone mineral density and decreased vitamin D metabolites
e. Prevention and screening of bone in persons with epilepsy
    i. Regular exercise

ii. Avoid smoking and limit alcohol intake to 2-3 drinks per day
iii. Screen vitamin D metabolites (25(OH)D)
iv. Consider DXA screening
v. If taking AED associated with bone loss i.e. cytochrome P450 enzyme inducing AEDs consider changing
vi. Understand risk of low bone mineral density (BMD) among persons with epilepsy

f. Calcium
   i. RDA for women 50 and younger: 1000 mg daily from all sources
   ii. RDA for women 51 years and older: 1200 mg daily from all sources
   iii. Calcium rich foods: Green leafy vegetables, oranges, figs, canned sardines and salmon with bones, canned shrimp, dairy, fortified foods
g. Vitamin D
   i. Vitamin D concentration
      1. Normal vitamin D: 25(OH)D concentration greater than 30 ng/mL (75 nmol/L)
      2. Vitamin D insufficiency: 25(OH)D concentration of 20 to 30 ng/mL (50 to 75 nmol/L)
      3. Vitamin D deficiency: 25(OH)D concentration less than 20 ng/mL (50 nmol/L)
   ii. Vitamin D supplementation in persons with epilepsy (Mikati et al. Neurology 2006;67(11):2005-2014)
      1. Adults treated with high (4000 IU per day) dose vitamin D supplementation had increased bone mineral density
      2. Children with low (400 IU per day) and high (4000 IU per day) had increased bone mineral density
h. Switching AEDs
   i. Prospective cohort of Thai males (Phabphal et al. 2013;Epilepsia 2013;54(6):e94-98.)
      1. Three groups:
         a. Phenytoin to levetiracetam
         b. Stopped phenytoin
         c. Continued phenytoin
      2. Patients who switched or stopped phenytoin had a significant increase in BMD at multiple sites and in 25(OH)D
      3. Patients who continued phenytoin had a significant decrease BMD at multiple sites and in 25(OH)D
i. AED and Osteoporosis Prevention Trial: Prospective 2-year double blind RCT of male veterans with epilepsy on AEDs (Lazzari et al. Epilepsia 2013;54(11):1997-2004.)

i. All enrolled participants (male veteran with epilepsy treated with either phenytoin, phenobarbital, sodium valproate, or carbamazepine for a minimum of 2 years) received calcium and vitamin D supplementation and were randomized to risedronate (an FDA approved bisphosphonate for osteoporosis) or matching placebo.
ii. Calcium and vitamin D supplementation or calcium and vitamin D supplementation in addition to risedronate improved BMD in more than 69% of male veterans with epilepsy who were taking AEDs. In the group receiving risedronate plus calcium and vitamin D there was a significant improvement of BMD at the lumbar spine as compared to the placebo group, which also received calcium and vitamin D. The use of risedronate plus calcium and vitamin D prevented the incidence of new vertebral fractures and one nonvertebral fracture in this cohort.