

Issues for Women with Epilepsy

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Issues arise at **all**
stages of a woman's life

Issues at all stages of a woman's life

- Adolescence/Young Adulthood
 - Menstruation/Fertility
 - Psychosocial issues
 - Seizure frequency
- Pregnancy
 - Pre-pregnancy planning, folate supplements
 - Pregnancy
 - Post-partum issues
- Menopause
 - Bone health

Adolescence

Issues in Adolescence

- Does epilepsy/AED affect:
 - Growth/height
 - Weight/BMI
 - Lipid metabolism (cholesterol, triglycerides)
 - Sexual maturation/fertility

Issues in Adolescence

- If a child is on AEDs during childhood, but stops them in adolescence and early adulthood there are no clear significant long term effects on health.
- Early on may have increased cholesterol, but normalizes after a few years and no lasting cholesterol effect.

Issues in Adolescence Growth/Height

- There is no difference in growth rate of final height of females on AEDs compared to controls.

Issues in Adolescence Obesity/Fertility

- If a child is started on an AED, especially Valproic Acid/Divalproex Sodium and continues it into adulthood, there is increase rate of
 - Obesity
 - Dyslipidemia
 - PCOS/Hyperadrenergic state
 - Hyperinsulinemia

Issues in Adolescence Seizure Frequency

- Seizure frequency may worsen or improve after/during adolescence.
- Not able to predict who will improve.
 - Childhood Absence should improve.
- May transiently worsen during puberty then settle after hormones are stabilized again.
- Doses of medication might need to be increased owing to growth.

Issues in Adolescence Psycho-Social

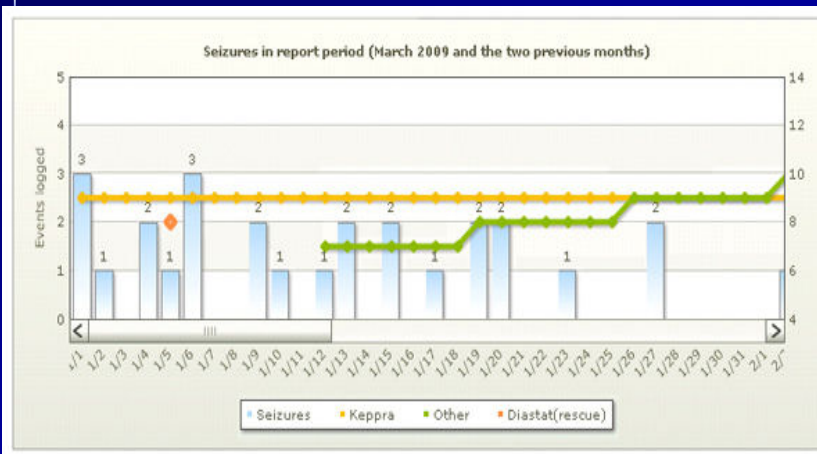
- Transition from dependence to independence, establishing goals.
- Sleep
- Alcohol and Drugs
- Medication
- Driving
- MD appointments

Issues in Adolescence Psycho-Social

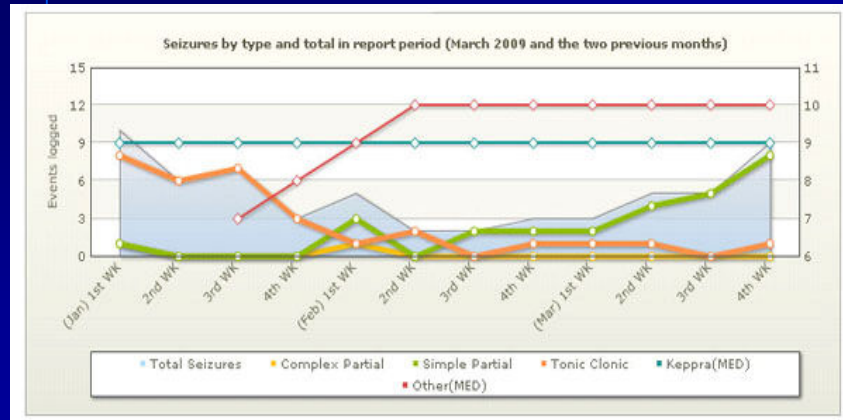
- Smartphone applications may help with medication reminders, and seizure log



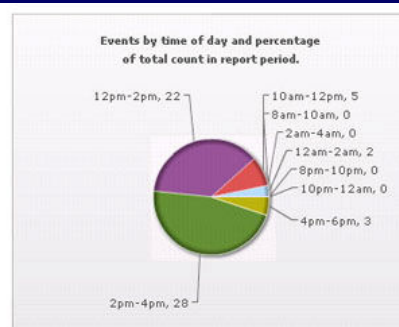
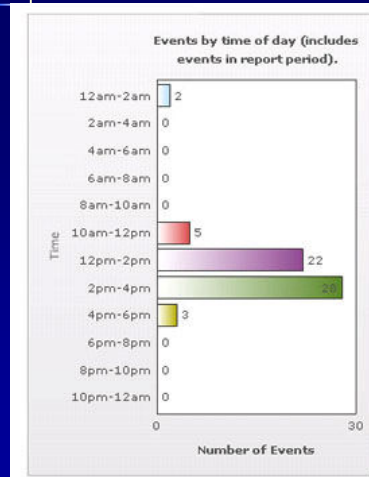
Issues in Adolescence Psycho-Social



Issues in Adolescence Psycho-Social



Issues in Adolescence Psycho-Social



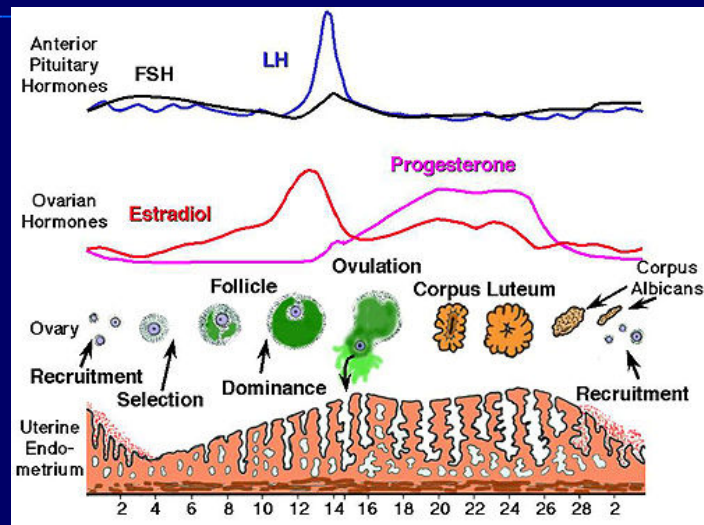
Total events in report period = 60

The Menstrual Cycle

The Menstrual Cycle

- Normal cycle 24-35 days (usual=28 days)
- Day 1= onset of menses
- Day 14= ovulation

The Menstrual Cycle



Epilepsy and Menstrual Cycle

- Seizure frequency can change during different parts of menstrual cycle
 - CATAMENIAL EPILPESY
- Menstrual cycle can become disordered due to epilepsy &/or anti-epileptic medications
 - ANOVULATION
 - POLYCYSTIC OVARY SYNDROME
 - PREMATURE MENOPAUSE

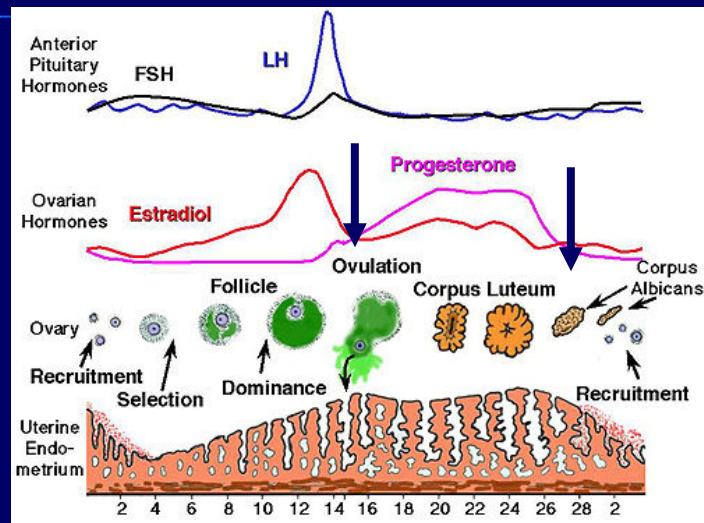
Catamenial Epilepsy

From the Greek "katamenios"
meaning "monthly"

Seizures and Hormone Fluctuations

- Many women report changes in seizure frequency and/or intensity related to menstrual cycle.
- Puberty can be time when seizures worsen or improve as can Menopause.
- Estrogens **LOWER** seizure threshold
→ more likely to have seizure
- Progestins **RAISE** seizure threshold
→ less likely to have a seizure

The Menstrual Cycle



Catamenial Epilepsy

- Patients report seizures related to menses 24-78% of the time.
- Usually
 - around ovulation
 - just prior to menses (-3-+3d)
- Anovulatory cycles quite common in epilepsy patients (up to 35% cycles vs 8% controls)
- Seizure 1.5x more frequent during anovulatory cycles

Diagnosis of Catamenial Epilepsy

- 1. Menstrual and seizure diaries
- 2. Characterization of whether cycle is ovulatory or not.
 - Document symptoms plus basal body temperature (look for rise in 0.7F after ovulation)
 - Take temperature first thing in AM.
 - Serum tests
 - Urine pregnanolol (may replace serum tests)

Management Catamenial Epilepsy

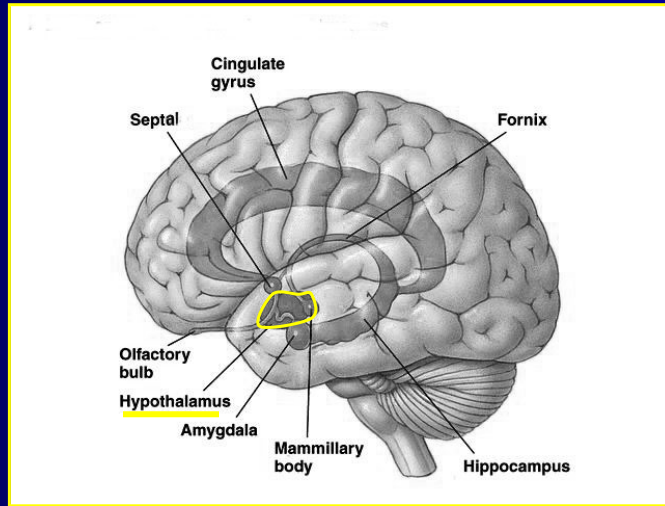
- Acetazolamide-tolerance
- Clobazam 20mg /day for 10 days (starting 2-4 days prior to menses or ovulation)
- Progesterone (synthetic or natural)
- Continuous oral contraceptive
- Overall, therapies not well studied and more research needs to be done
- Talk to Neurologist and Gynecologist for best management plan.

Menstrual Disorders

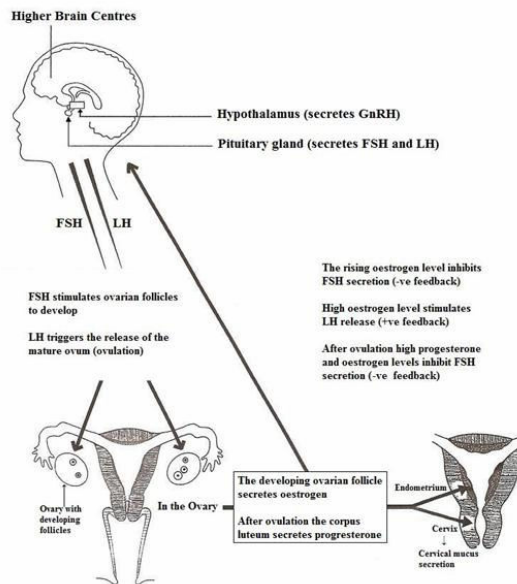
Menstrual Disorders

- Abnormal neuroendocrine regulation → **Hypothalamus/pituitary**
- Abnormal peripheral synthesis and metabolism of steroid hormones and binding globulins → **Ovary**
- Gonadal toxicity of some AEDs → **Ovary**

Hypothalamus and Hippocampus



Regulation of Hormones (Feedback Mechanism)



Women with epilepsy have a higher incidence of **menstrual disorders** than general population

- Epilepsy (48%) vs Controls (30%)
- More common in women with **high seizure frequency (>5sz/year)**
- More common in women on **multiple Anti-Epileptic Drugs**
- More common in women on **Valproate** than Carbamazepine.

Anovulatory Cycles

- Women with Idiopathic Generalized Epilepsy (27.1%)-
- Women with Focal Epilepsy (14.3%)
- Controls (10%)
- Recent (within last 3 years)users of Valproate (38%) vs non-recent users (10.7%)

Anovulatory Cycles

- Can cause infertility
- Can increase seizure frequency

Polycystic Ovary Syndrome (PCOS)

- **Chronic anovulation**
 - infertility
- **Hyperandrogenic state** (relative increase in testosterone vs estrogen)
 - Increase facial hair/acne
 - Alopecia (hair loss)

Polycystic Ovary Syndrome (PCOS)

- Prevalence General Population
– 4-11%
- Prevalence Women with Epilepsy
– 10-26%

Epilepsy and PCOS

- Brain activity related to epilepsy (especially temporal lobe epilepsy) can affect hypothalamus and pituitary gland.
- This could effect hormone secretion in brain.

AEDs and PCOS

- Studies suggest that **Valproate** has high association with PCOS in epilepsy patients (60%), vs 33% in carbamazepine, 14% other drugs.
- VPA more likely to be associated with PCOS if patient started drug in childhood or adolescence.
- PCOS can reverse or improve when VPA switched for another AED.

Symptoms of PCOS

- Anovulatory cycles- mid-cycle bleeding
- Increased facial hair
- Increased acne
- Weight gain

- **Let your physician know if you are experiencing these symptoms.**

Prevention of PCOS

- Avoid VPA in young women **if possible**.
- **BUT** VPA is a very good drug for certain types of epilepsy.
- Juvenile Myoclonic Epilepsy and intractable epilepsy may require VPA therapy.
- **Decision to be made with you and your doctor on individual basis.**

Premature Menopause

- Menopause occurs **earlier** in women with highest seizure frequency (up to 3-4 years earlier than avg 51) and who have used many AEDs over a lifetime.
- Menopause can cause increase or decrease in seizure frequency (**30% increase, 30% decrease, 30% no change**).

Seizures and Menstrual Cycle

- Every patient is different
- Keep a seizure calendar and menstrual calendar
- Talk to your doctor

Contraception

Some Seizure Medications can reduce effectiveness of Oral Contraceptive

- "Enzyme Inducing" Medications: cause P450 system in liver to metabolize hormones faster → reduces amount of hormone circulating.
 - Carbamazapine
 - Oxcarbazepine
 - Phenytoin
 - Phenobarbitol/Primidone
 - Topiramate (doses above 200mg/day)
 - Rufinamide
 - Perampanel
- Need at least 50µg of ethinyl estradiol or mestanil AND back-up barrier method of contraception.
- Lamotrigine level is lowered by OCP

Some Seizure Medications can reduce effectiveness of Oral Contraceptive

- **NO** interactions with the following drugs:
 - Levetiracetam
 - Valproic Acid
 - Lacosamide
 - Pregabalin
 - Gabapentin

Seizure Medications and Oral Contraceptive

- Levonorgestral/Depo-provera is an alternative, but if using enzyme-inducers its efficacy is still reduced.
 - Injection every 10 weeks instead of every 12 weeks.
- Oral contraceptive is still better than a barrier method alone for prevention of pregnancy.

Seizure Medications and Mirena IUD

- The influence of these medicines on the contraceptive efficacy of MIRENA has not been studied, but it is not believed to be of major importance due to the mainly local mechanisms of action (taken directly from product monograph).

Folic Acid

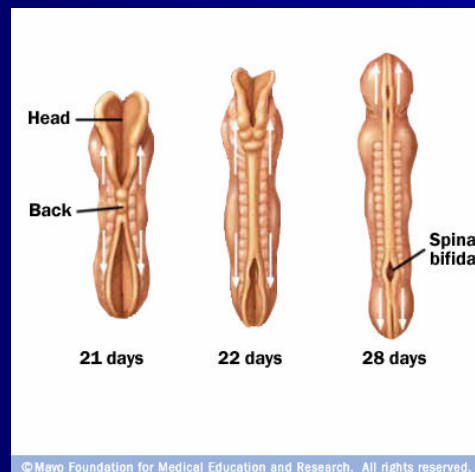
Folic Acid: benefits

- 50% of all pregnancies unplanned.
- Folic acid has been shown to reduce neural tube defects, such as spina-bifida, in the general population
- Some evidence suggests that it reduces risk of childhood brain tumors and Acute Lymphocytic Leukemia
- Evidence that perinatal exposure associated with higher fetal IQ (at age 6- NEAD)
- Canada: since started fortifying food with Folic Acid (150ug/100g) in 1998- (NEJM 2007)
 - Overall 46% reduction in live births with spina bifida

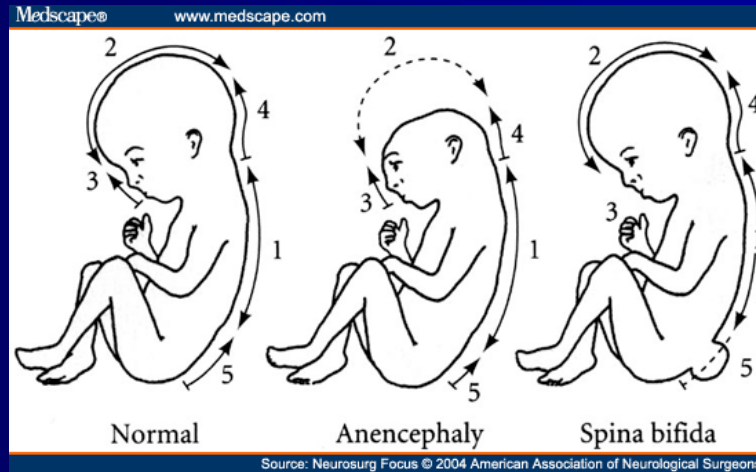
Folic Acid: benefits

- Neural tube develops in first 4 weeks of pregnancy, so critical development occurs before a woman knows she is pregnant.
- All women of child-bearing age should be taking at least 0.4mg folic acid/day

Neural Tube Development



Closure of neural tube



Folic Acid: benefits

Do women with Epilepsy need more?

VPA- 2-5% of births will have NTD- spina bifida

CBZ 0.5-1% of births will have spina bifida

Not as robust a relationship to NTD with other AEDs

Other risks for NTD: previous pregnancy with NTD or family history, ethnicity, IDDM, vit deficiencies, obesity

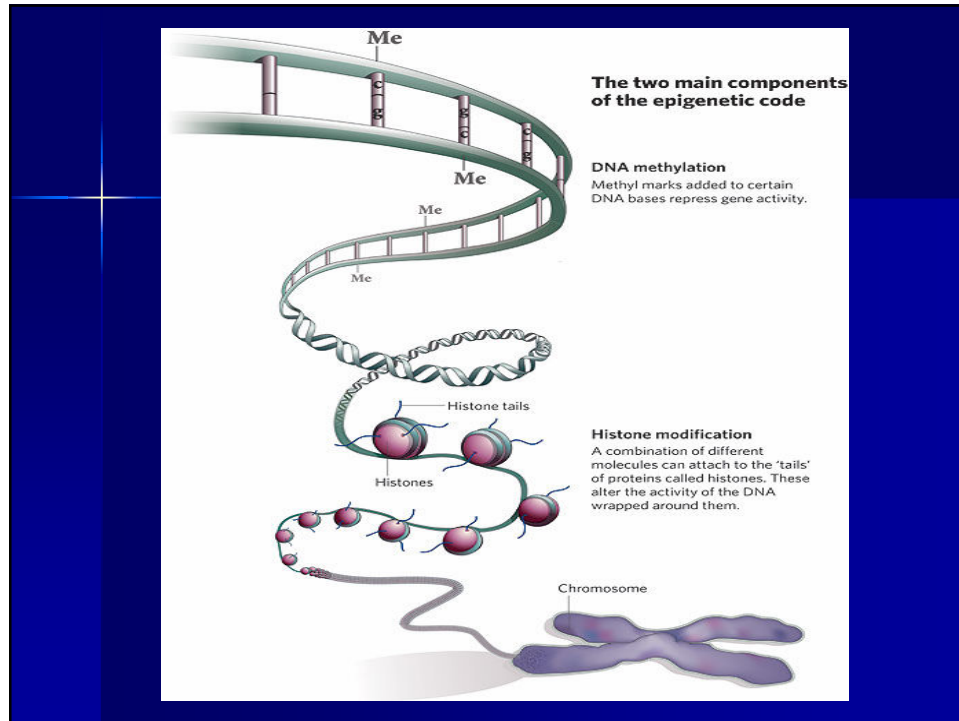
There is a case to be made that if you are taking VPA or CBZ a higher dose of Folic acid may help: 1mg-5mg. Most MD recommend 5mg. **No good evidence for dosing.**

Folic Acid: Any risks?

- If someone already has and established colon or prostate CA, then folic acid supplement may hasten the growth of the cancer.
- If someone has no colon Ca, folate supplements may prevent development of cancer.

Folic Acid: Any risks?

- DNA methylation is an important **epigenetic** determinant in gene expression, in the maintenance of DNA integrity and stability, in chromosomal modifications, and in the development of mutations.
- ⑩ **Epigenetics**= changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence, hence the name epi- (Greek: over; above) -genetics
- Aberrant patterns and dysregulation of DNA methylation are related to colorectal carcinogenesis.



Folic Acid: Any risks?

- Theoretical risk that too much folic acid may lead to aberrant methylation and may lead to genetic predisposition to cancers.
- Fine balance because too little folate can do the same..

Folic Acid Take Home

- All women of childbearing age should be on at least 0.4mg-1mg /day folic acid. Prenatal vitamins have 1mg Folic Acid.
- Theoretical reasons to think that increase dose 4-5mg for people on VPA and CBZ.
- Unclear if other AEDs warrant higher doses Folate- at least 0.4- 1mg/day.
- Further studies needed to determine optimal dosing in women with epilepsy.

Pregnancy

Epilepsy is not a contraindication to pregnancy

- 90% of pregnant women with epilepsy deliver healthy newborns.
- There is an increased rate of complications in women with epilepsy.
- Multidisciplinary approach is important and close follow-up is needed
 - family doctor,
 - obstetrician
 - neurologist

Issues Related to Pregnancy

- Seizure control
- Risks of drugs and seizures to fetus

Seizure Control During Pregnancy

Primary Goal: **Optimal Seizure Control**

- Risk to fetus of generalized tonic-clonic seizure is of hypoxia and acidosis
 - Increase risk of abruptio placenta, miscarriage, stillbirth, blunt trauma, intracranial hemorrhage.
- Unclear whether complex partial seizures or absence seizures pose risk to fetus

Changing AED before pregnancy

- If patient is on drug with high teratogenic risk **CHANGE SHOULD BE MADE 6 months PRIOR to pregnancy.**
- Do not start changing drugs once patient is pregnant because of high risk of breakthrough seizures and time-window of embryo development is past.

Discontinuing AEDs before pregnancy

- Seizure-free 2-5 years
- Single seizure type
- Normal neuro exam and normal IQ
- Normal EEG on medication
- **This process should be complete 6 months prior to conception**

Care During Pregnancy

- Most women have no change in seizure frequency during pregnancy. Only 15-33% had increased seizures
- Increased seizures could relate to
 - Hormonal changes
 - Decreased drug levels due to increased blood volume, decreased absorption,
 - Decreased compliance
 - Sleep deprivation
 - Increased stress/anxiety

Care During Pregnancy: Drug levels

- Monitor drug levels at each trimester
- More frequent monitoring for patients with breakthrough seizures or missing doses.
- Lamotrigine levels need to be tested monthly as levels can drop quickly during pregnancy.

Fetal Malformations

Care During Pregnancy: Types of Fetal malformations

- Types of Malformations
 - Congenital (require medical or surgical intervention, cause major functional problems)
 - Most common orofacial clefts, cardiac defects, urogenital
 - Rate is 4-6% in infants of women with epilepsy vs 2-3% in general population
 - Minor Abnormalities (no major intervention required)
 - Intrauterine growth retardation/hypertelorism
 - Rate 30% in infants of women with epilepsy vx 15% in controls

Care During Pregnancy: Other factors contributing to malformations

- Having seizures during first trimester
- Alcohol/drug use
- Malnutrition (i.e: folate deficiency)
- Genetics
 - Family history of neural tube defects
 - Previous pregnancy with neural tube defect
 - Diabetes Mellitus

Care During Pregnancy: Factors Affecting Malformations-AEDs

- Higher Doses may increase risk
- Polytherapy worse than monotherapy (4.5% vs 7.5% rate of congenital malformations)
- Specific Drugs used:
 - VPA and Carbamazepine*
 - Lamotrigine and Valproate*
 - Carbamazepine + Phenobarbital+/-Phenytoin

Risks of fetal Malformations

DRUG USAGE	INCIDENCE OF MAJOR MALFORMATIONS
Any AED	7.86%
Lamotrigine alone	2.1-2.9%
Carbamazepine alone	2.0-5.2%
Phenobarbitol alone	4.7-6.5%
Phenytoin alone	3.4-10.5%
Levetiracetam	0.7% <i>*new</i> /6.47%
Topiramate	3.8-4.8%
Valproic acid alone	8.6-16.7%
Untreated	0.8-5.0%
General population	1.6-2.2%

Newer Drugs

- No monotherapy data on:
 - Lacosamide
 - Pregabalin
 - Oxcarbazepine
 - Rufinamide

Topiramate

- UK Pregnancy Registry (2008)
 - 208 pregnancies (178 live births)
 - 16 Major Congenital Malformations, 3 in monotherapy (4.8%) and 13 in polytherapy (11.2%).
 - 4 (2.2%) oral clefts, 4 hypospadias.
 - Oral cleft rate 11x background population rate

Topiramate

- North American Pregnancy Registry (2011)
 - 289 live birth (TPX monotherapy) vs 372 controls
 - 3.8% Major Congenital Malformations vs 1.3% unexposed reference group
 - Relative Risk (RR) 2.8 versus 1.3 for Lamotrigine and 2.2 for Carbamazepine
 - Cleft palate (4, 2 isolated) = 0.69% (background prevalence 0.07%) = 10x higher
 - Low birth weight (<2500g) was 9.8% (vs 3.6% controls)= RR 2.7. The degree of low birth weight was NOT significant for LTG or CBZ

Topiramate

- **North American Pregnancy Registry (2011)**
- **Summary:**
 - Higher rate of oral cleft and low birth weight in babies born to women on TPX monotherapy versus LTG, CBZ and controls.
 - Unclear if this is causal or related to other factors in that patient population.

Care During Pregnancy: **Risks of cognitive Effects on children (age 6) of women on AEDs- NEAD Study**

- USA and UK, 1999-2004, pregnant women on monotherapy with CBZ/VPA/LTG/PHT
 - F/U at 3 years and 6 years published
- VPA is independent predictor of lower than expected child IQ. Other most important predictor is mother's IQ.
- Effect is inversely proportional to dose
- Effect is for verbal and non-verbal indicators, across main domains of cognitive function by age 6.
- Some suggestion that CBZ and LTG at higher doses may have effect on verbal IQ
- Periconceptional folate has positive effect on IQ.

Newer AEDs and infant cognition

- Valproic acid compared to Levetiracetam (Keppra)
 - up to 24 months of age no risk to children exposed to Levetiracetam in utero.
- Unclear cognitive effects of oxcarbazepine, topiramate, lacosamide,

Care During Pregnancy: Screening for fetal malformations

- 14-16 weeks: maternal **serum alpha-fetoprotein**
- **Ultrasound** 16-20 weeks
- Together these tests have 95% sensitivity to detect open neural tube defects, 85% to detect cardiac defects
- **Amniocentesis** if equivocal results: increases sensitivity to 99%

Care During Pregnancy: AED management

- *If possible*
 - Monotherapy
 - Lowest effective dose

Care During Pregnancy: Vitamin K supplementation

- May be increase risk of **hemorrhagic disease of the newborn** in babies of mothers on enzyme-inducing AEDs: mortality of 30% for baby if affected
- Vit K 1mg IM to the baby at birth.

Post-Partum Care

Breast Feeding

- Some AEDs more than others are secreted to some extent in breast milk
- Most experts believe that benefits of breast feeding outweigh risks of AED
- **Leviteracetam, Primidone have highest concentration in breast milk**
- **LTG, gabapentin and topiramate next highest**
- **VPA/CBZ/phenytoin/phenobarbital amounts in breast milk felt not to be clinically significant.**
- Not many studies done on this do determine if there are any long-term negative effects.

Breast Feeding

- NEAD Study (Nov 2010)
- Compared IQ in children up to age 3 exposed in utero and breast milk to one of the following: Phenytoin, Carbamazepine, Lamotrigine, Valproic Acid.
- Compared to group exposed in utero but NOT breast fed.
- No significant differences in IQ at age 3.
- Follow-up age 6 pending.

Breast Feeding- Norwegian Study

- Early Child Development and Exposure to Antiepileptic Drugs Prenatally and Through Breastfeeding- A Prospective Cohort Study on Children of Women With Epilepsy *JAMA Neurol.* 2013;70(11):1367-1374.
- Prenatal exposure to antiepileptic drugs was associated with impaired fine motor skills already at age 6 months, especially when the child was exposed to multiple drugs. There were no harmful effects of breastfeeding. **Women with epilepsy should be encouraged to breastfeed their children irrespective of antiepileptic drug treatment**

Care of the Child

- Lots of anxiety about risks to child under supervision of mother with epilepsy
- Fear of falls/dropping baby, drowning, burns etc.
- Not much published research in this area.
- Education is key and depends on type of seizures and baseline cognitive function.

More research needed

- North American Antiepileptic Drug Pregnancy Registry

**AED PREGNANCY
REGISTRY
TOLL FREE:
1-888-233-2334**

Menopause

- **Perimenopause:** onset of irregular menses with or without hot flashes.
- **Menopause:** 1 year without menstruation
- **Perimenopause** associated with an increase in seizures, especially in those who had catamenial epilepsy pattern.
- During perimenopause may be relatively more estrogen than progesterone leading to increased seizures.
- **Post-menopause:** 30% less sz, 30% unchanged and 30% increased sz.

Bone Health

Women with Epilepsy at Increased Risk for Osteoporosis/Fractures

- Risk of menopause : earlier onset in patients with epilepsy
- Risk of decreased mobility in epilepsy patients
- Risk of AEDs
 - Decreased Vitamin D levels because of liver induction→decreased bone formation
 - Phenytoin, Phenobarbital, Mysoline, carbamazepine, benzodiazepines and VPA definitely lead to decreased bone density despite normal Vit D levels, but mechanisms not clear.
 - Newer AEDs may be associated with bone loss (Mr. Os study) but not well studied.

Women with Epilepsy at Increased Risk for Osteoporosis/Fractures

- Mechanism of bone loss is not clear
 - “Induction” model: Enzyme-Inducing AED increase function of hepatic enzymes→accelerates metabolism of Vit D3→decreased calcium absorption→increased PTH→increased bone resorption→higher rate bone loss.
 - Direct effect on bone?
 - EIAED/Lev/VPA/GBP on bone cells
 - GBP→increased norepinephrine release→activate osteoblast adrenergic receptor→can decrease osteoblast numbers and reduce bone formation

Other factors that decrease bone density

- Cigarette smoking
- Excessive alcohol intake
- Glucocorticoids
- Estrogen deficiency
- Low body weight
- Caucasian or asian ethnicity
- Low calcium diet

Management of Bone Health

- Calcium Recommended Dietary intake
 - Age 19-50 1000mg/day
 - Women >51: 1200mg/day
 - Men>70: 1200mg/day
- Vitamin D Recommended Dietary Intake All patients (age 9-70 male and female)
 - Vit D 600 –4000 IU /day.
 - Adult 70 and older should get minimum 800IU

Summary

- Women with Epilepsy have specific issues that need to be addressed
- Occur at all points in life cycle
- Contraception/Menstrual Cycle
- Pregnancy
- Menopause/Bone Health

Summary

- We are still learning
- Don't be afraid to ask questions of your doctor!

Thank You!

Questions

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