

Women and Pregnancy Issues in Epilepsy

Cleveland Clinic Epilepsy Update and Review
September 24, 2020

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Objectives: Review issues related to pregnancy in women with epilepsy including contraception, outcomes and seizure control

Epilepsy Birth Control Registry Web-based Survey

- 1,144 WWE in the community, 18-47 years
- 79% had at least 1 unintended pregnancy (65% of all)

Relative risks of unintended pregnancy by contraception type

Epilepsy Birth Control Registry Web-based Survey

Relative risks of unintended pregnancy by hormonal contraception status

CYP3A 4 inducers increase sex steroid metabolism and risk of ovulation/contraceptive failure

Inducers

Carbamazepine
Clobazam
Eslicarbazine*
Felbamate*
Lamotrigine*
Oxcarbazepine
Perampanel*
Phenobarbital
Phenytoin
Primidone
Rufinamide*
Topiramate*

Non-Inducers

Brivaracetam
Ezogabine
Ethosuximide
Gabapentin
Lacosamide
Levetiracetam
Pregabalin
Tiagabine
Valproate
Vigabatrin
Zonisamide

* Weak inducers

Hormonal contraceptives increase clearance of glucuronidated AEDs

- Combined OC/LTG 300 mg/d
- ↓ LTG AUC by 52%
- ↓ LTG C_{max} by 39%
- Gradual ↑LTG in pill-free week
- LTG dose adjustment often necessary when introducing or withdrawing hormonal therapies

Contraception without AED Interactions

- Long-acting reversible contraceptives (LARC)- preferred
 - Intrauterine devices
 - Progestin implant
 - Depot medroxyprogesterone acetate (MPA)
- Barrier methods
- Fertility awareness-based methods
- Sterilization

Adverse Pregnancy Outcomes in Offspring of Women with Epilepsy

- Major congenital malformations – structural abnormalities interfering w/function/require major intervention
- Minor anomalies – structural deviations not interfering w/health
- Developmental delay
- Low birth weight
- Prematurity
- Microcephaly
- Stillbirth
- Epilepsy

Pregnancy Outcomes over Recent Decades in 283 Women with Epilepsy

	1970s	1980s	1990s
Major malformation %	19.5	9.6	3.5
Monotherapy, %	34.2	63.5	74.4
Folic acid (TM1) %	27.8	43.2	82.7

FDA Pregnancy Categories

- Category A: Adequate/well-controlled studies failed to demonstrate risk to fetus in TM1 (no evidence in later TMs)
- Category B: Animal studies failed to demonstrate risk to fetus and no adequate/well-controlled studies in pregnant women
- Category C: Animal studies show adverse effect on fetus and no adequate/well-controlled studies in humans, but potential benefits outweigh potential risks
- Category D: Positive evidence of human fetal risk based on investigational/marketing experience, but potential benefits may outweigh potential risks
- Category X: Animals or humans demonstrate fetal abnormalities and/or positive evidence of human fetal risk based on investigational/marketing experience, and risks in pregnant women clearly outweigh potential benefits

AED Pregnancy Categories

Category C

- | | |
|--|---|
| <ul style="list-style-type: none">• Clobazam• Brivaracetam• Eslicarbazepine• Ethosuximide• Ezogabine• Felbamate• Gabapentin• Lacosamide | <ul style="list-style-type: none">• Lamotrigine• Levetiracetam• Oxcarbazepine• Perampanel• Pregabalin• Rufinamide• Tiagabine• Vigabatrin |
|--|---|

Category D

- | |
|---|
| <ul style="list-style-type: none">• Carbamazepine• Clonazepam• Phenobarbital• Phenytoin• Primidone• Topiramate• Valproate |
|---|

New FDA Pregnancy/Lactation Labeling Information

- Effective June 2015
- Manufacturers have 3 yr to remove pregnancy category
- Information reorganized
- Elimination of standardized risk and letter categories
- New subsection “Females and Males of Reproductive Potential” including pregnancy testing, contraception, infertility

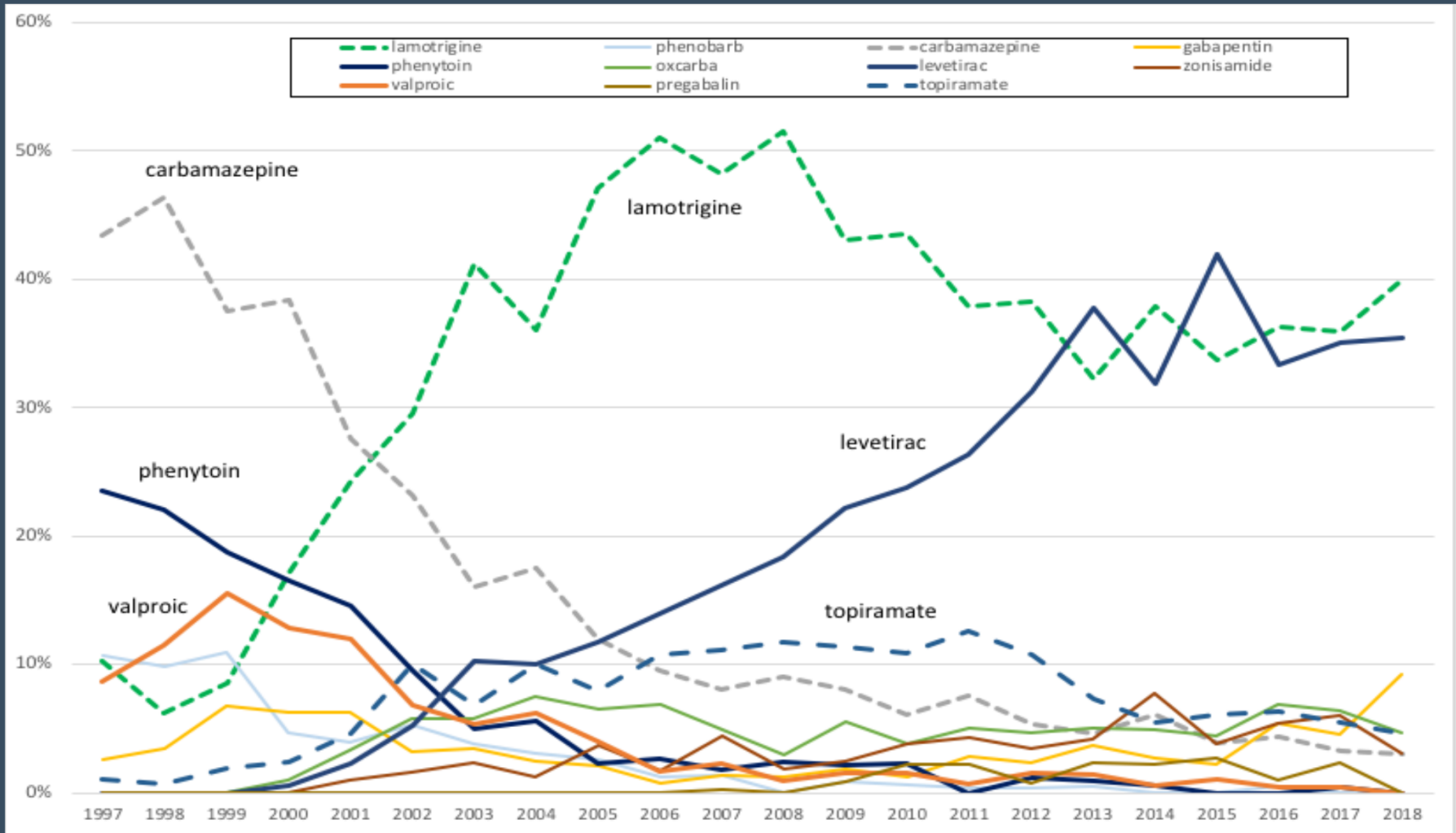
North American AED Pregnancy Registry

- Launched in 1997 in US, Canada
- Patient initiated
- Follow-up at 7 months gestation, postpartum
- Comparison groups
 - External: 1.6% at 5 d among 69,277 enrolled
 - Internal: 532 friends/family of enrollees
 - LTG TM1
 - Unexposed (without epilepsy, no AEDs)
- 10,200 enrollees including >6000 monoRx exposures

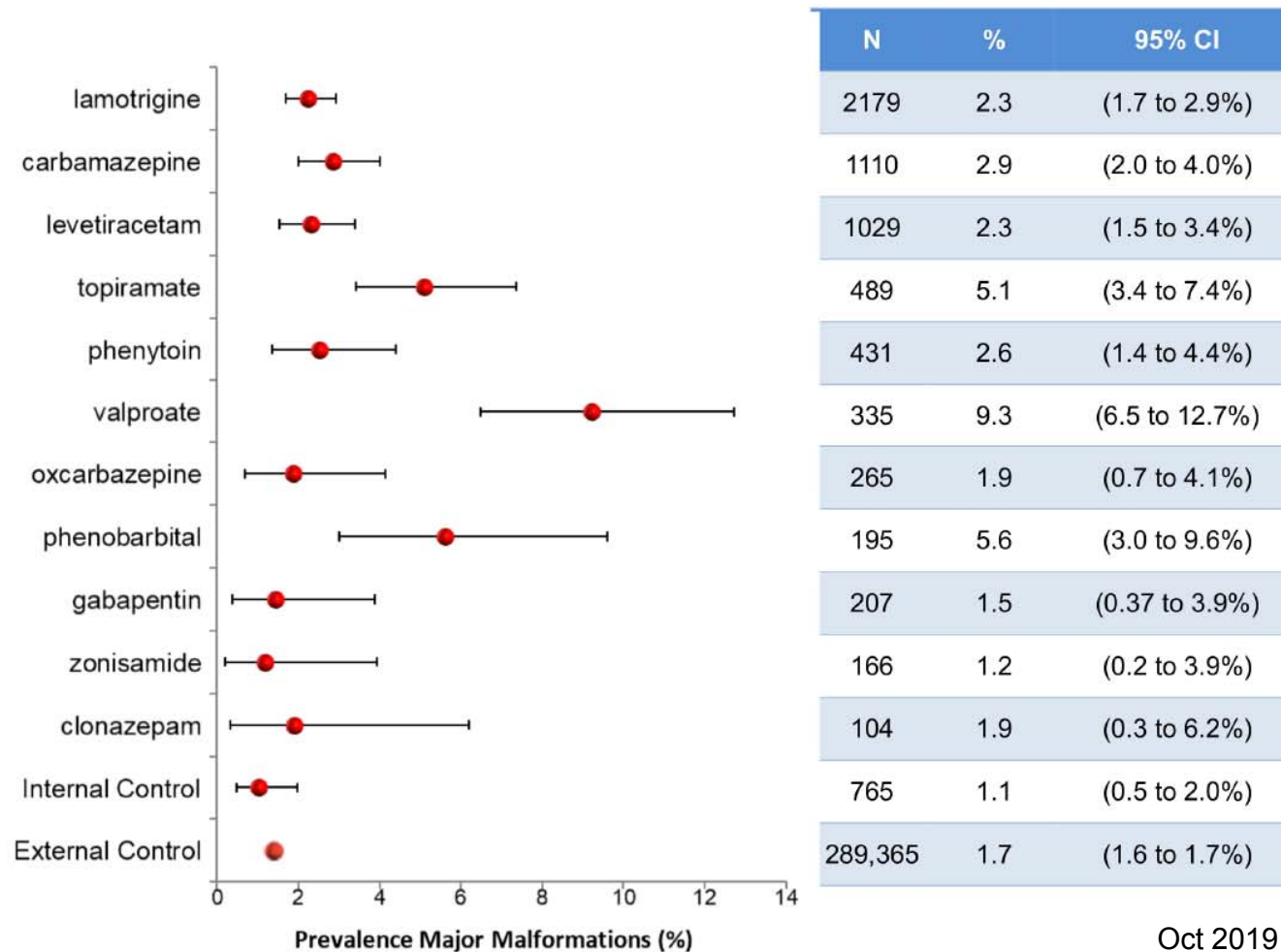


888-233-2334

NA AED: Trends of Enrollment for Specific AEDs



Prevalence of Major Malformations



Oct 2019

MCM risk varies by AED combination

MCM % (95% CI)

	Monotherapy	Polytherapy without VPA	Polytherapy with VPA
LTG¹	1.9 (1.3-2.8)	2.9 (1.6-4.8)	9.1 (3.4-19.0)
CBZ¹	2.9 (2.0-4.0)	2.5 (1.1-4.6)	15.4 (6.5-29.3)
LTG²	2.2 (1.6-3.1)	2.8 (1.5-5.0)	10.7 (6.4-17.0)

¹Holmes HB. *Arch Neurol* 2011; doi:10.1001; ²Cunnington MC. *Neurology* 2011;76;1817-1823.

EURAP Registry

- Launched in 1999
- 45 countries worldwide
- Physician initiated
- Follow-up each TM, birth and 1 yr postpartum on-line
- 26,753 enrolled; 15,220 prospective, 80% monoRx
- Most common AEDs: LTG, CBZ, VPA; 321 combinations
- MCM rate 4.8%; monoRx 4.4%; polyRx 6.5%
- 12% detected perinatally, 60% at birth, 28% in by yr 1



EURAP: MCM Prevalence by Monotherapy

EURAP: MCM Prevalence by Monotherapy

RESEARCH ARTICLE

Open Access



Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes

Areti Angeliki Veroniki¹, Elise Cogo¹, Patricia Rios¹, Sharon E. Straus^{1,2}, Yaron Finkelstein^{3,4,5}, Ryan Kealey¹, Emily Reynen¹, Charlene Soobiah^{1,6}, Kednapa Thavorn^{7,8,9}, Brian Hutton^{7,10}, Brenda R. Hemmelgarn¹¹, Fatemeh Yazdi¹, Jennifer D'Souza¹, Heather MacDonald¹ and Andrea C. Tricco^{1,12*}

96 studies involving 58,461 patients

Risks associated with Specific Monotherapies

Meta-analysis findings

- **Carbamazepine:** overall major/minor CM
- **Clobazam:** IUGR, preterm birth
- **Ethosuximide:** overall major CM, cleft, club foot
- **Gabapentin:** cardiac, hypospadias
- **Phenobarbital:** overall major CM, IUGR, cleft
- **Phenytoin:** overall major CM, cleft, club foot
- **Topiramate:** overall major CM, fetal loss, IUGR, cleft
- **Valproate:** overall major/minor CM, fetal loss, hypospadias, cleft, club foot

ILAE 2019: MCM Prevalence for monotherapies

Developmental Risks of AED Monotherapy

29 cohort studies including 5100 infants/children

- Cognitive delay: VPA (OR 7.4)
- Autism
 - LTG (8.9)
 - OXC (OR 13.5)
 - VPA (OR 17.3)
- Psychomotor delay: VPA (OR 4.2)

Mechanisms of AED Teratogenicity

- Toxic intermediary metabolites
 - Epoxide formation: PHT, CBZ
 - Epoxide hydrolase inhibition: VPA
- Folate deficiency
- Hypoxia/Reoxygenation
 - PHT, CBZ, PB, Trimethadione
- Apoptosis
- Genetic susceptibility
 - Placental transfer, absorption, metabolism, distribution, receptor binding
 - Folate metabolism
 - Antioxidant compounds

Seizure Control in 5000 Pregnancies: EURAP & Kerala Registries

- 48-67% seizure free
- Relapse higher for:
 - Focal vs. generalized epilepsy (OR 1.6)

Pre-pregnancy seizure control is the most important predictor of seizure control during pregnancy

- month (OR 15)
- LTG monoRx
 - GTCs
 - Increased drug dose

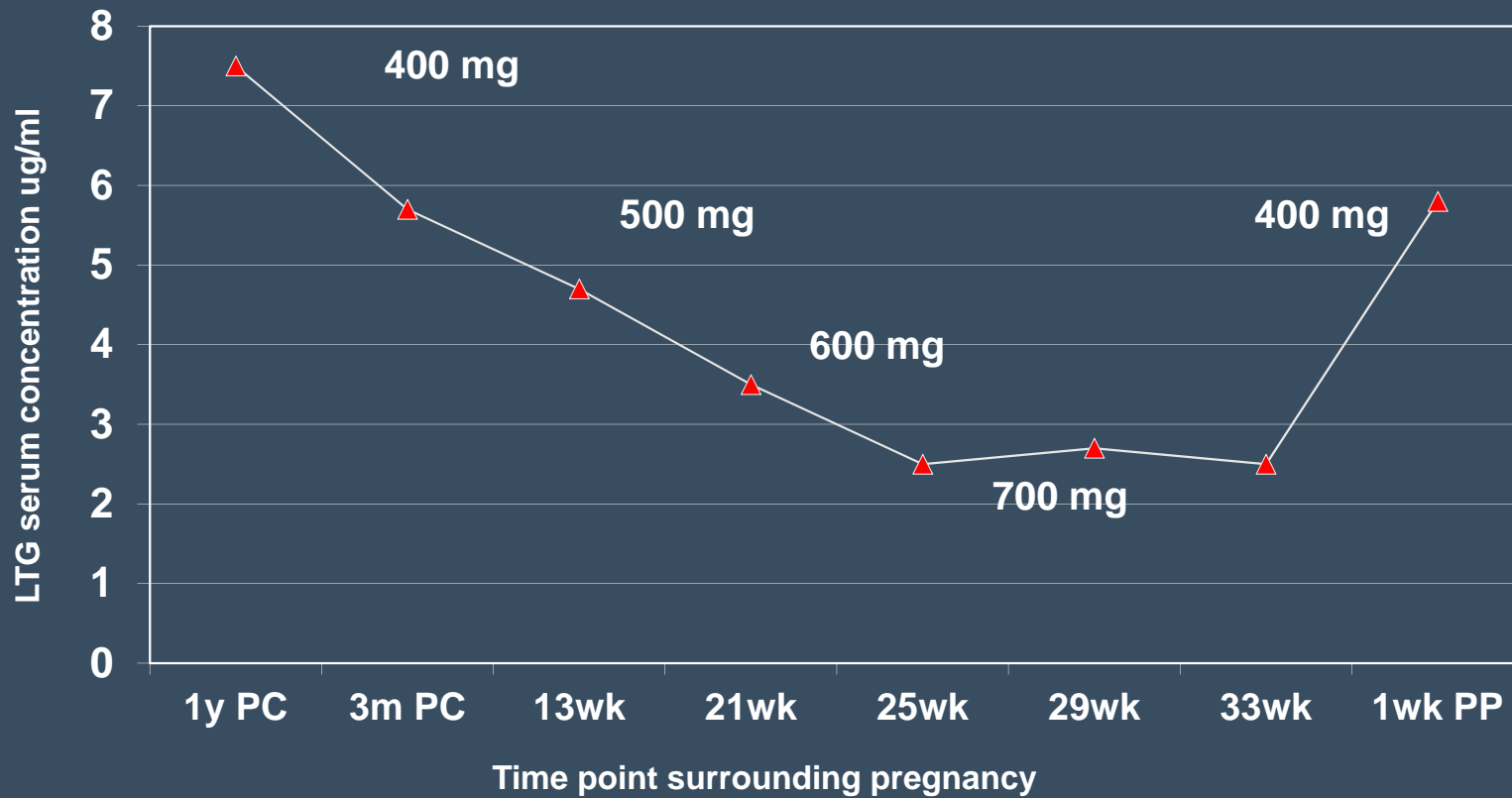
Causes of Seizures during Pregnancy

- Alterations in AED pharmacokinetics
 - Declining plasma proteins
 - Increased hepatic metabolism – P450, glucuronidation
 - Increased renal clearance
 - Increased volume of distribution
- Medication noncompliance
- Stress
- Sleep deprivation
- Hyperemesis gravidarum

Convulsive seizures -> fetal hypoxia, heart rate decelerations, miscarriage, stillbirth
Nonconvulsive seizures -> abdominal trauma

AED Clearance and Seizure Control in 115 Pregnancies

Sarah 24 yr with Generalized Epilepsy on LTG



Therapeutic Drug Monitoring in Pregnancy

- No Class 1 evidence
- Need/frequency of monitoring should be individualized
- Pronounced decline/worsening seizures for drugs eliminated by glucuronidation (LTG, OXC); reversion to baseline within days of delivery
- Less need for monitoring for drugs w/minor alterations in free concentration (CBZ, VPA)
- Unpredictable, potentially significant decline in LEV associated w/seizures
- Decline >35% associated w/increased risk of seizures

Breastfeeding in Women with Epilepsy

- Breast milk penetration inversely proportional to protein binding
- Impaired hepatic elimination of LTG and OXC in
- No harmful effects on IQ at 3 yr
- No association w/adverse development at 6-36 mo
- Association b/w maternal & neonatal LTG concentrations

Boxplots of percentage of infant-to-mother plasma concentrations showing median and 25/75th percentiles. Whiskers represent 1.5 times IQR. Circles not connected by vertical lines or lying on horizontal whiskers are outliers.

2009 AAN Epilepsy Physician Performance Measure Counseling for Women of Childbearing Potential

- Counsel WWE (12-44 yr) about epilepsy and treatment effects on contraception/pregnancy
- Document in EMR at least annually
- Document medical reason for not counseling (e.g. sterile)
- Provide information about contraception, conception, pregnancy, breastfeeding before sexual activity/pregnancy
- Discuss decreased effectiveness of OCPs with EIAEDs
- Discuss risks of seizures/MCM with AED therapy in pregnancy
- Annual review including bone health, contraception, how pregnancy/menopause affect seizures

Management Strategies for Pregnancy and Epilepsy

- Repeated preconception counseling
- Individualized contraceptive counseling –IUDs preferred
- Use most effective AED at lowest possible dose
- Avoid VPA (most teratogenic risk) and PB, PHT, TPM (intermediate risk) if possible
- Avoid unnecessary polyRx and drug changes post conception
- Individualize therapeutic monitoring
- Folic acid 1-5 mg per day preconception
- Encourage breastfeeding

Resources for Women with Epilepsy

- AAN practice parameter 2009 update
www.aan.com/go/practice/guidelines
- North American AED Pregnancy Registry
www.aedpregnancyregistry.org
- EFA Women & Epilepsy Initiative
www.efa.org
- EURAP
www.eurap.org

