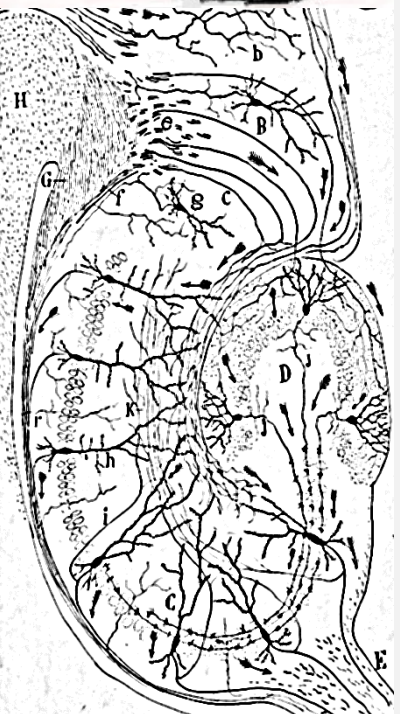


Epilepsy in Pregnancy

P. Emanuela Voinescu, MD, PhD

Brigham and Women's Hospital

Harvard University

Update on Neurology and Psychiatry of Women

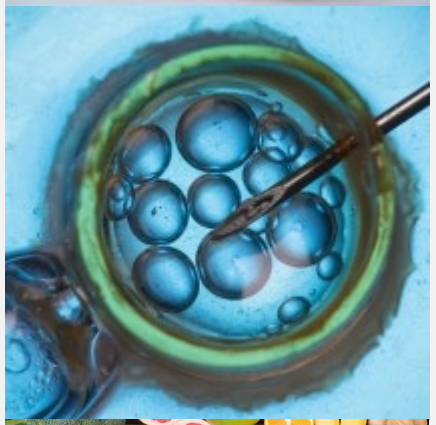
May 24, 2024

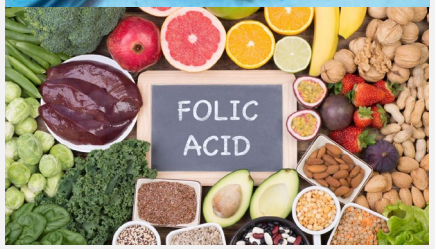
Disclosures

- Board Chair of My Epilepsy Story, a non-profit organization for women with epilepsy
- Scientific Advisor for the North American AED Pregnancy Registry
- Honoraria for:
  - Online Lecture for Brainwork.md: "Management of epilepsy during pregnancy"
  - Moderator for a Neurodiem Workshop: "Epilepsy and family planning: what are the challenges for neurologists?"
  - CME Lecture for Physicians' Education Resource
  - Grand Rounds from Stony Brook University
  - CME Courses from Harvard Medical School
  - Presenter and SIG Organized for American Epilepsy Society

Personalized Care for Women at Different Biological Stages

PRECONCEPTION





- Fertility
- Contraception
- Folic acid supplementation

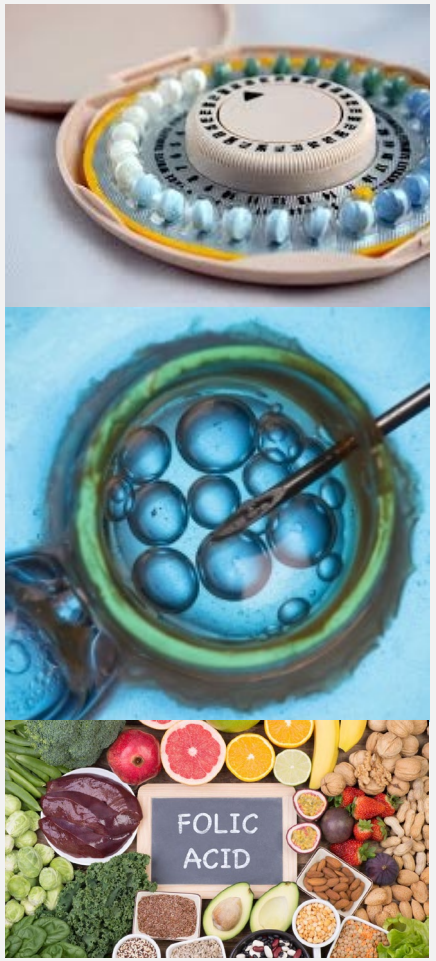
PREGNANCY

- Structural and cognitive teratogenicity
- Neonatal/Obstetrical outcomes
- Pharmacokinetic considerations

POSTPARTUM

- Seizure provoking factors
- Pharmacokinetic considerations
- Breastfeeding

PRECONCEPTION



- Fertility
- Contraception
- Folic acid supplementation

Preconception PLANNING

1. Ensure **adequate** contraception **(check interactions with ASMs)**
2. Recommend folic acid **(1mg daily)**; consider prenatal vitamin supplementation
3. **Clarify the** diagnosis: non-epileptic vs epileptic; focal vs generalized; known etiology?; surgical?
4. Optimize ASM regimen for seizure control and pregnancy outcome:
    1. Consider switching to an ASMs with a better pregnancy outcome profile
    2. Monotherapy preferred to polytherapy
    3. Reduce to minimal effective dose
    4. If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, PB, TPM)
5. Determine **individualized therapeutic** ASM baseline concentration (ASM concentration on the minimal effective dose)

ASM, antiseizure medication; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; TPM, topiramate; VPA, valproic acid.
Voinescu PE and Pennell PB. *Semin Neurol.* 2017;37:611–623. Voinescu, P.E., Meador, K.J. *Curr Obstet Gynecol Rep.* 2022

Reproductive health and Fertility

- Reports of higher rates of PCOS and anovulation in WWE[1]
- Studies suggest lower birthrate in WWE (Finland) [2]
- Many factors could lower birth rates (lower marriage rates, libido, ovulation) - "Ideal World" survey of Epilepsy Action UK women found that 33% not considering having children because of their epilepsy[3]

1. Harden C, Pennell PB. *Lancet Neurol* 2013; 2. Artama M, *Am J Epidemiol* 2004; 3. Crawford P, Seizure 2003.

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3 Site Study
BWH (Dr. Pennell)
LIJH (Dr. Harden)
NYU (Dr. French)

Pennell PB, et al. *JAMA Neurology* 2018.

Prospective cohort observational study

Healthy control women (n=100)
Women with epilepsy on AEDs

- LTG monotherapy (n=33)
- LEV monotherapy(n=33)
- EIAEDs (n=100)

Results:

*WWE and healthy controls seeking pregnancy had **comparable** ovulatory rates, likelihood and time to achieve pregnancy, pregnancy outcomes*

Reproductive health and Fertility

- Many studies suggest lower birthrate in WWE – biological or choice?
- USA: state laws allowed forcible sterilization of WWE until 1956[1]
- UK: people with epilepsy were not allowed to marry until 1970[1]
- India: epilepsy was grounds for annulment of marriage until 1999[2]

1. WHO. Epilepsy: social consequences and economic aspects; fact sheet 166. 2001; 2. D'Souza C. Epilepsy and discrimination in India. Neur Asia 2004; 9:53.

Women with Epilepsy Pregnancy Outcomes and Deliveries
WEPOD

Pennell PB, et al. *JAMA Neurology* 2018.

Prospective cohort observational study – 3 sites:

Healthy control women (n=108)
Women with epilepsy on ASMs (n=89)
- LTG monotherapy (n=39)
- LEV monotherapy (n=25)
- Strong EI-ASMs mono/polytherapy (n=16)

Results:

*WWE and healthy controls seeking pregnancy had **comparable** ovulatory rates, likelihood and time to achieve pregnancy, pregnancy outcomes*

Prospective cohort observational study:

No control group
Women with epilepsy (n=375)
- Most frequently used ASMs: carbamazepine, valproate, phenobarbital, phenytoin

Results:

38.4% WWE had infertillity
Important predictors: polytherapy, PB use, older age and lower education

Kerala Registry of Epilepsy and Pregnancy (1998-2007)

Sukumaran SC, et al. *Neurology* 2010

Choosing the right contraception

Degree of induction of metabolism of sex steroid hormones	Strong inducers	Weak inducers	Noninducers
Antiepileptic drug	Phenobarbital Phenytoin Carbamazepine Primidone Oxcarbazepine Perampanel	Topiramate Lamotrigine[a] Felbamate Rufinamide Clobazam Eslicarbazepine	Ethosuximide Valproate Gabapentin Clonazepam Tiagabine Levetiracetam Zonisamide Pregabalin Vigabatrin Lacosamide
Recommended contraceptive methods	IUD Depo-provera	IUD Progestin implant Depo-provera [b] Some OCPs	IUD, Progestin implant, Depo-provera, OCPs, Patches, Vaginal Rings

IUD offers a solution for all, OCPs are still an option for many WWE

Voinescu PE and Pennell PB. *Semin Neurol* 2017

Choosing the right contraception

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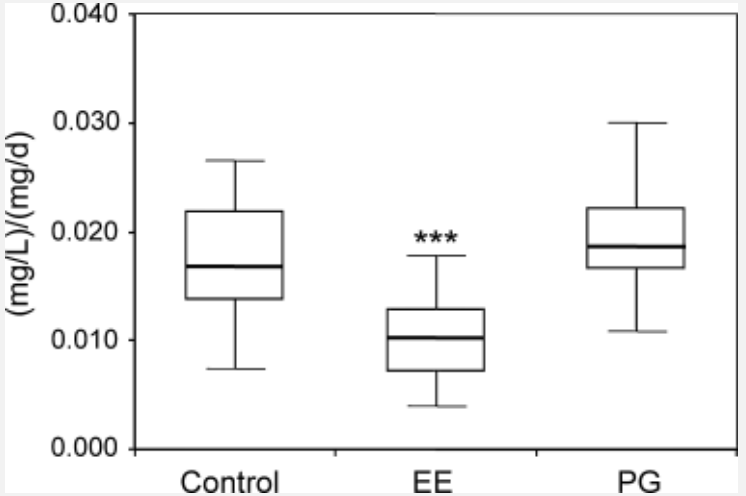
Recommended contraceptive methods	IUD Depo-provera	IUD Progestin implant Depo-provera [b] Some OCPs	IUD, Progestin implant, Depo-provera, OCPs, Patches, Vaginal Rings

Lamotrigine only modestly decreases progestin concentration without evidence of ovulation, thus it is **safe to be used with low dose OCPs.**

Voinescu PE and Pennell PB. *Semin Neurol* 2017

Lamotrigine and contraceptives

- LTG concentration lower with combined OCPs[1]
- EE, not PG, decreases LTG concentration[2]
- New baseline LTG concentration - reached at 8.0 (SD 3.69) days after the starts of OCPs[3]



COCs are effective with LTG, but LTG dose likely needs to be increased.

EE, ethinyl estradiol; LTG, lamotrigine; OCP, oral contraceptive pills; PG, progesterone; SD, standard deviation.

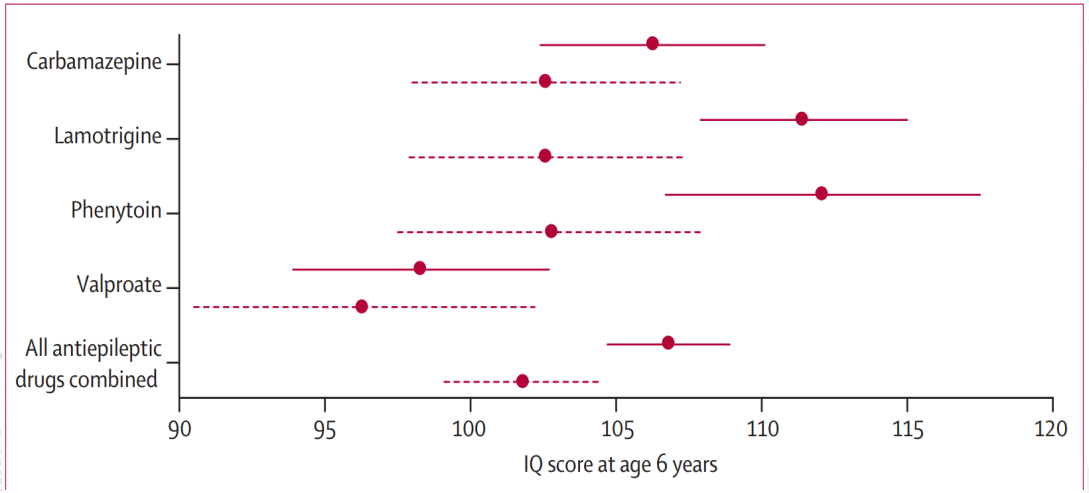
1. Sabers A et al. Neurology. 2003;61:570-571. 2. Reimers A et al. Epilepsia. 2005; 46(9):1414-1417. 3. Wegner I et al. Neurology 2009;73(17):1388–93.

Recommend folic acid supplementation

- Reduced risks of MCMs in the general population[1]
- Neurodevelopmental benefits in children exposed to AEDs in utero

- Higher IQ scores with supplementation in pregnancy[2]

- Lower risk of autistic traits [3]



Mean (95% CIs) are shown for **folate (solid lines)** and **no folate (dashed lines)**.

Table 2. Risk of Autistic Traits in Association With FAS Stratified by Maternal AED Treatment

Trait or FAS Status	Maternal Epilepsy With AED Exposure	Maternal Epilepsy Without AED Exposure	No Maternal Epilepsy
Autistic traits, No. (%) without/with FAS			
18 mo[a]	11 (32.4)/15 (8.8)	5 (8.9)/18 (9.5)	1294 (8.9)/3723 (6.8)
36 mo[b]	9 (25.7)/8 (5.8)	2 (4.9)/4 (2.5)	725 (6.2)/1665 (4.2)
OR (95% CI) for FAS vs no FAS by age			
18 mo			
Crude	5.0 (2.0-12.2)	0.9 (0.3-2.6)	1.4 (1.3-1.4)
Adjusted model 1[c]	5.0 (2.0-12.3)	0.9 (0.3-2.7)	1.3 (1.2-1.4)
Adjusted model 2[d]	6.2 (2.4-16.1)	1.0 (0.4-3.0)	1.3 (1.2-1.4)
Adjusted model 3[e]	5.9 (2.2-15.8)	NA	NA
36 mo			
Crude	5.7 (2.0-16.1)	2.0 (0.4-11.2)	1.7 (1.6-1.9)
Adjusted model 1[c]	7.1 (2.4-21.2)	2.0 (0.3-12.6)	1.7 (1.6 - 1.9)
Adjusted model 2[d]	7.6 (2.5-23.5)	2.5 (0.4-16.6)	1.7 (1.5-1.9)
Adjusted model 3[e]	7.9 (2.5-24.9)	NA	NA

AEDs, antiepileptic drugs; MCMs, major congenital malformations.

1. Werler MM et al. JAMA. 1993;269:1257-1261. 2. Meador K et al. Lancet Neurol. 2013;12(3):244–52. 3. Bjørk M et al. JAMA Neurol. 2018;75(2):160–168.

Research

JAMA Neurology | Original Investigation

Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy

Håkon Magne Vegrim, MD; Julie Werenberg Dreier, PhD; Silje Alvestad, MD, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Jannicke Igland, PhD; Maarit K. Leinonen, MD, PhD; Torbjörn Tomson, MD, PhD; Yuelian Sun, MD, PhD; Helga Zoega, MA, PhD; Jakob Christensen, MD, PhD, DrMedSci; Marte-Helene Bjørk, MD, PhD

- Observational study, thus association and not causation; always the potential of a missed confounding factor
- Large study, yet a rare disease and only 18 cases of pediatric cancer in this cohort
- The average folate dose for mothers with epilepsy on ASM was 4.3mg daily; they establish that a dose of 3mg was associated with a similar risk

The benefits of folic acid ≤ 3mg supplementation likely outweigh the risks

JAMA Neurol. doi:10.1001/jamaneurol.2022.2977
Published online September 26, 2022.

Prevalence of highly effective contraception use by women with epilepsy

Andrew G. Herzog, MD, Hannah B. Mandle, MPH, and Devon B. MacEachern, BS

Neurology® 2019;92:e2815-e2821. doi:10.1212/WNL.0000000000007581

Correspondence
Dr. Herzog
aherzog@bidmc.harvard.edu

Abstract

Objective

To determine (1) the proportion of women with epilepsy (WWE) at risk of unintended pregnancy who use highly effective contraception, (2) demographic predictors, and (3) folic acid (FA) use.

Methods

These cross-sectional data come from 311 US WWE, 18–47 years, who participated in the Epilepsy Birth Control Registry (EBCR) web-based survey in 2017. They provided demographic, epilepsy, antiepileptic drug (AED), contraceptive, and FA data. We report frequencies of highly effective contraception use and use logistic regression to determine demographic predictors. We report the proportion who take FA.

Results

A total of 186 (59.8%) of the 311 WWE were at risk of unintended pregnancy. A total of 131 (70.4%) used a highly effective contraceptive category; 55 (29.6%) did not. An additional 13 (7.0%) used a combination of generally effective hormonal contraception with an enzyme-inducing AED, which poses increased risk of unintended pregnancy. Overall, 68 (36.6%) of the 186 WWE at risk did not use highly effective contraception. Increasing income ($p = 0.004$) and having insurance ($p = 0.048$) were predictors of highly effective contraception. A total of 50.0% took FA supplement. There was no significant difference in relation to the use or lack of use of highly effective contraception.

Conclusion

A total of 36.6% of WWE in the EBCR did not use highly effective contraception and 50.0% did not take FA in 2017 despite the important negative consequences of unintended pregnancy on pregnancy outcomes. There is a need for more readily available information and counseling on safe and effective contraception and FA use for this community.

Preconception PLANNING

1. Ensure **adequate** contraception **(check interactions with ASMs)**
2. Recommend folic acid **(1mg daily)**; consider prenatal vitamin supplementation
3. **Clarify the** diagnosis: non-epileptic vs epileptic; focal vs generalized; known etiology?; surgical?
4. Optimize ASM regimen for seizure control and pregnancy outcome:
    1. Consider switching to an ASMs with a better pregnancy outcome profile
    2. Monotherapy preferred to polytherapy
    3. Reduce to minimal effective dose
    4. If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, PB, TPM)
5. Determine **individualized therapeutic** ASM baseline concentration (ASM concentration on the minimal effective dose)

ASM, antiseizure medication; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; TPM, topiramate; VPA, valproic acid.
Voinescu PE and Pennell PB. *Semin Neurol.* 2017;37:611–623. Voinescu, P.E., Meador, K.J. *Curr Obstet Gynecol Rep.* 2022

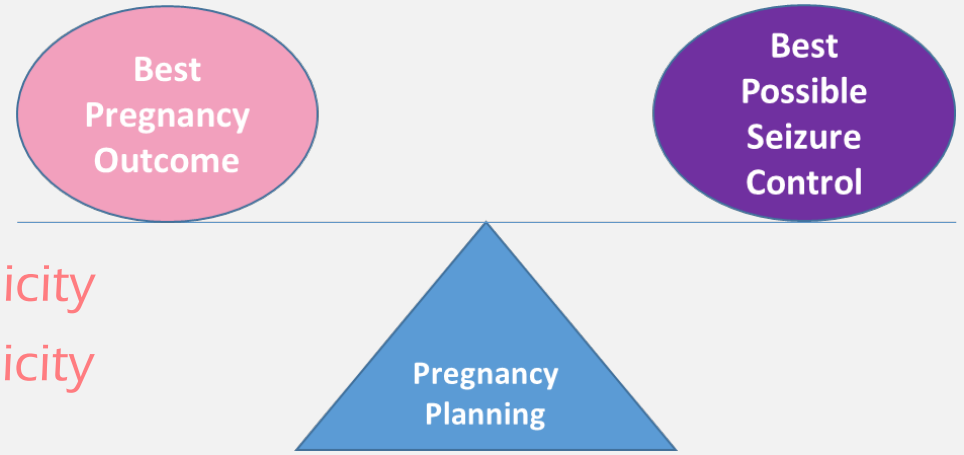
PREGNANCY

- Structural and cognitive teratogenicity
- Neonatal/Obstetrical outcomes
- Pharmacokinetic considerations

Antiseizure medications and pregnancy

Education regarding the risk of ASMs and risk of seizures is important

Personalized equation: Benefits versus risks of ASM during pregnancy



Risk of medications

- Structural teratogenicity
- Cognitive teratogenicity
- Neonatal outcomes

Risk of seizures

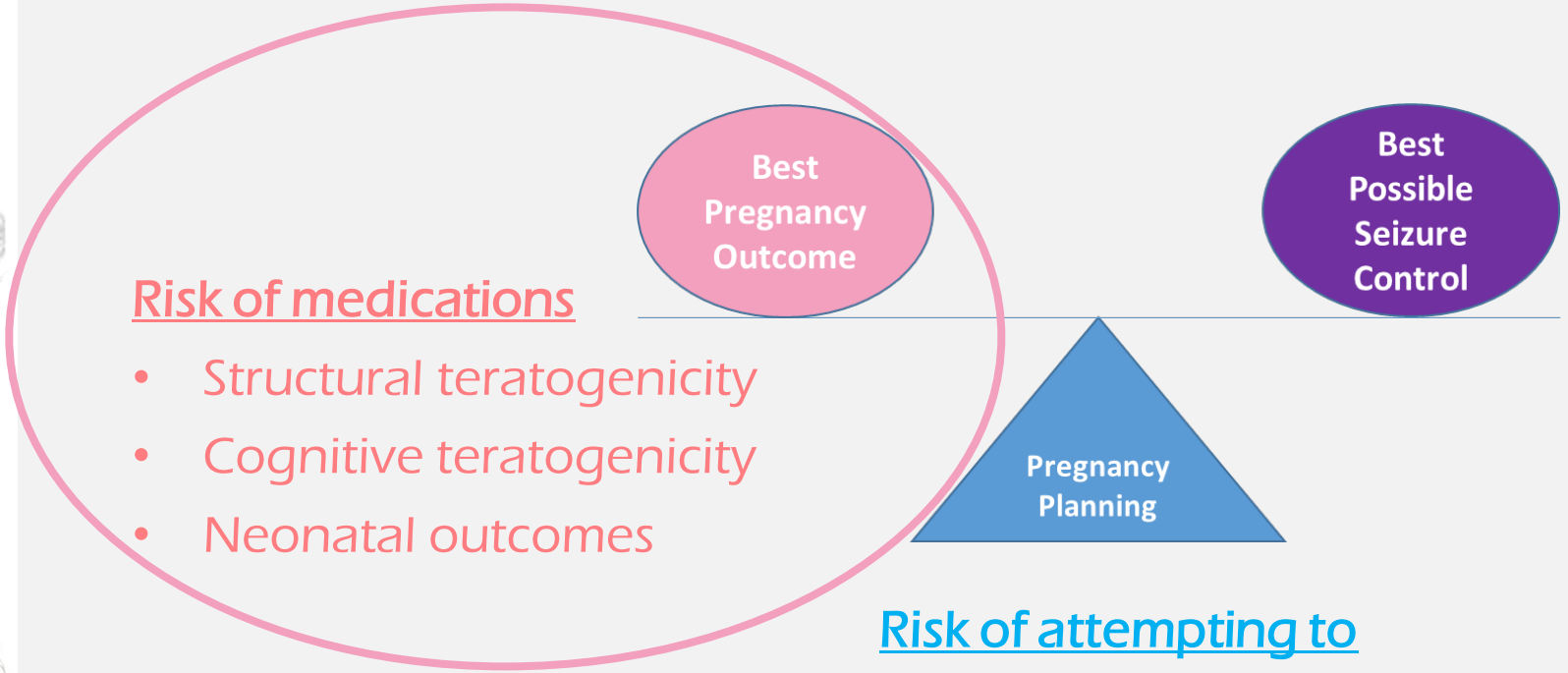
- On the mother
- On the fetus

Risk of attempting to optimize the ASM regimen

- Seizure control
- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

Personalized equation: Benefits versus risks of ASM during pregnancy



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Risk of seizures

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- On the fetus

Risk of attempting to optimize the ASM regimen

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- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

Timing of certain MCMs

Tissues	Malformations	Postconceptional age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d
Genitourinary	Hypospadias	84 d

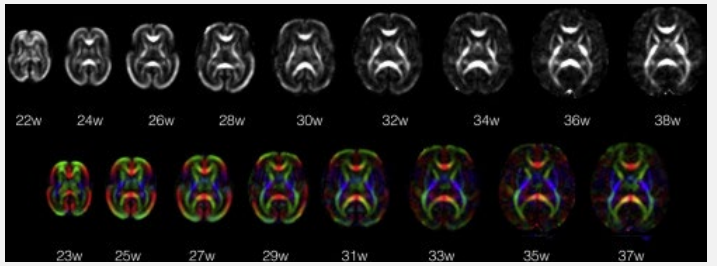
Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic!

CNS, central nervous system; MCMs, major congenital malformations.
http://www.columbia.edu/itc/hs/medical/humandev/2004/Chpt23-Teratogens.pdf

PREGNANCY

Structural Teratogenicity

Neurodevelopmental Effects



Summary of ASM structural & neurodevelopmental effects

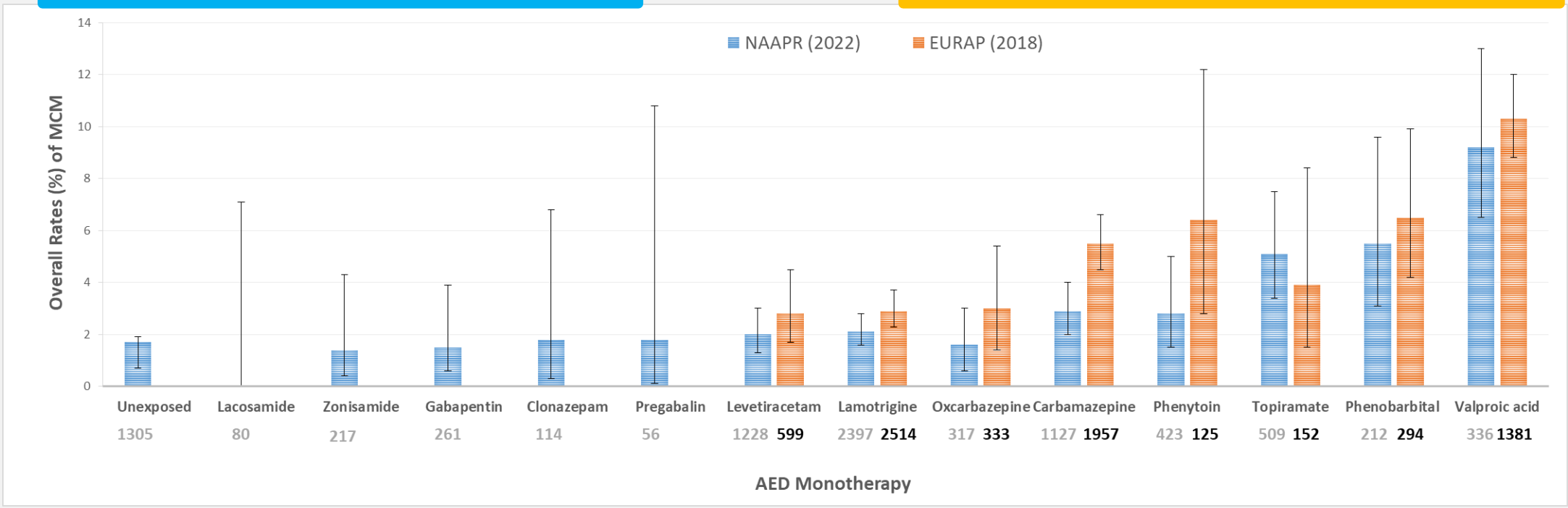
- Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic – **Planned pregnancy is key!**
- Rate of MCMs with exposure to ASM monotherapy - green with no noticeable impact and red with negative impact on neurodevelopment
  - Low: **LTG, LEV,** OXC, ZNS, (LCM, GBP)
  - Medium: **CBZ, PHT** (CLZ)
  - High: **TPM, PB, VPA**
- Rate of SGA – higher for TPM, PB >ZNS
- Optimize ASM regimen for seizure control and pregnancy outcome:
  - Consider switching to an ASM with a better pregnancy outcome profile
  - Monotherapy preferred to polytherapy
  - Reduce to minimal effective dose
  - If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, TPM)

ASM, antiseizure medication; CBZ, carbamazepine; CLZ, clonazepam; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; MCM, major congenital malformations; OXC, oxcarbazepine; SGA, small gestational age; PB, phenobarbital; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

Voinescu PE and Pennell PB. Semin Neurol. 2017;37:611–623.

Comparative Safety of ASMs During Pregnancy

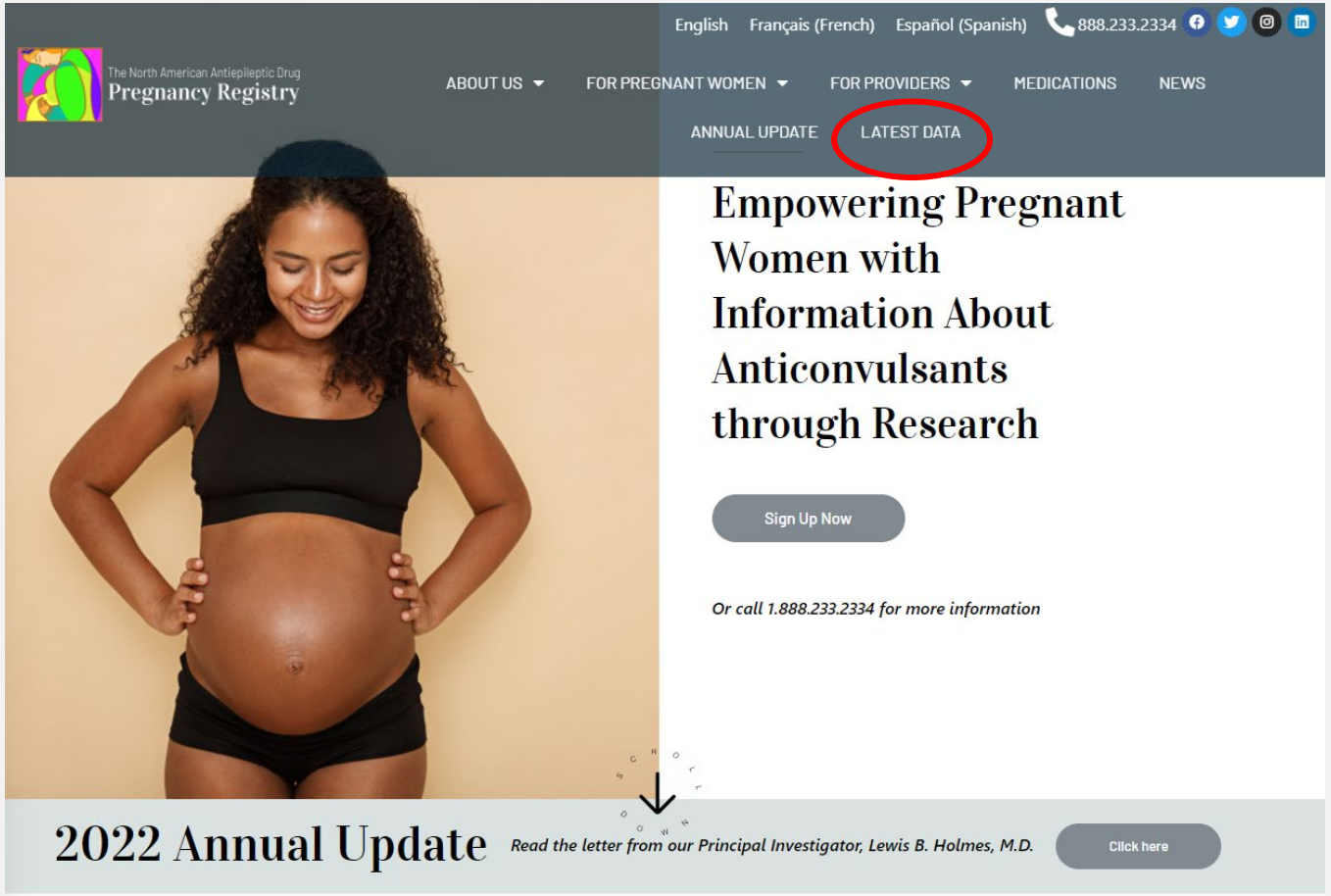
THE NORTH AMERICAN ANTIEPILEPTIC DRUG PREGNANCY REGISTRY



ASM, antiseizure medication; EURAP, European Registry of Antiepileptic drugs and Pregnancy; NAAPR, North American Antiepileptic Drug Pregnancy Registry; MCM, major congenital malformation.

Hernandez-Díaz et al. *Neurology*.aedpregnancyregistry.org/wp-content/uploads/The-NA-AED-Pregnancy-Registry-AES-2020.pdf; Tomson 2012;78(21):1692–1699 – unpublished updated: https://wwwet al, *The Lancet Neurology*. 2018;17(6):530–538.

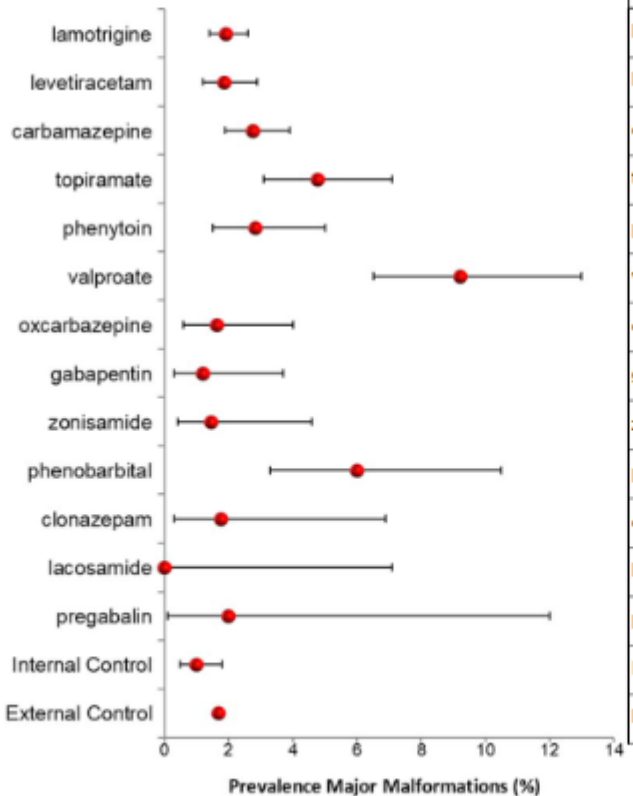
NAAPR



www.aedpregnancyregistry.org

Latest Study Data - January 2023

Risk of malformations for specific AED in monotherapy 1st trimester and the control groups



	N	%	95% CI
lamotrigine	2333	1.9	(1.4 to 2.6%)
levetiracetam	1179	1.9	(1.2 to 2.9%)
carbamazepine	1122	2.8	(1.9 to 3.9%)
topiramate	503	4.8	(3.1 to 7.1%)
phenytoin	423	2.8	(1.5 to 5.0%)
valproate	336	9.2	(6.5 to 13%)
oxcarbazepine	304	1.6	(0.6 to 4.0%)
gabapentin	251	1.2	(0.31 to 3.7%)
zonisamide	205	1.5	(0.4 to 4.6%)
phenobarbital	200	6.0	(3.3 to 10.5%)
clonazepam	113	1.8	(0.3 to 6.9%)
lacosamide	64	0.0	(0 to 7.1%)
pregabalin	50	2.0	(0.1 to 12%)
Internal Control	1201	1.0	(0.5 to 1.8%)
External Control	289,365	1.7	

Dose-Dependent Risk for Certain ASM Monotherapies

	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)	p value
Lamotrigine				
≤325 mg/day	1870	46	2·5% (1·8–3·3)	0·0145
>325 mg/day	644	28	4·3% (2·9–6·2)	..
Carbamazepine				
≤700 mg/day	1276	58	4·5% (3·5–5·8)	0·0140
>700 mg/day	681	49	7·2% (5·4–9·4)	..
Valproate				
≤650 mg/day	600	38	6·3% (4·5–8·6)	<0·0001
>650 to ≤1450 mg/day	666	75	11·3% (9·0–13·9)	..
>1450 mg/day	115	29	25·2% (17·6–34·2)	..
Phenobarbital				
≤80 mg/day	73	2	2·7% (0·3–9·5)	0·0390
>80 to ≤130 mg/day	161	10	6·2% (3·0–11·1)	..
>130 mg/day	60	7	11·7% (4·8–22·6)	..

When a dose dependency for the risk of major congenital malformation was identified, comparisons also included specific dose ranges at time of conception.

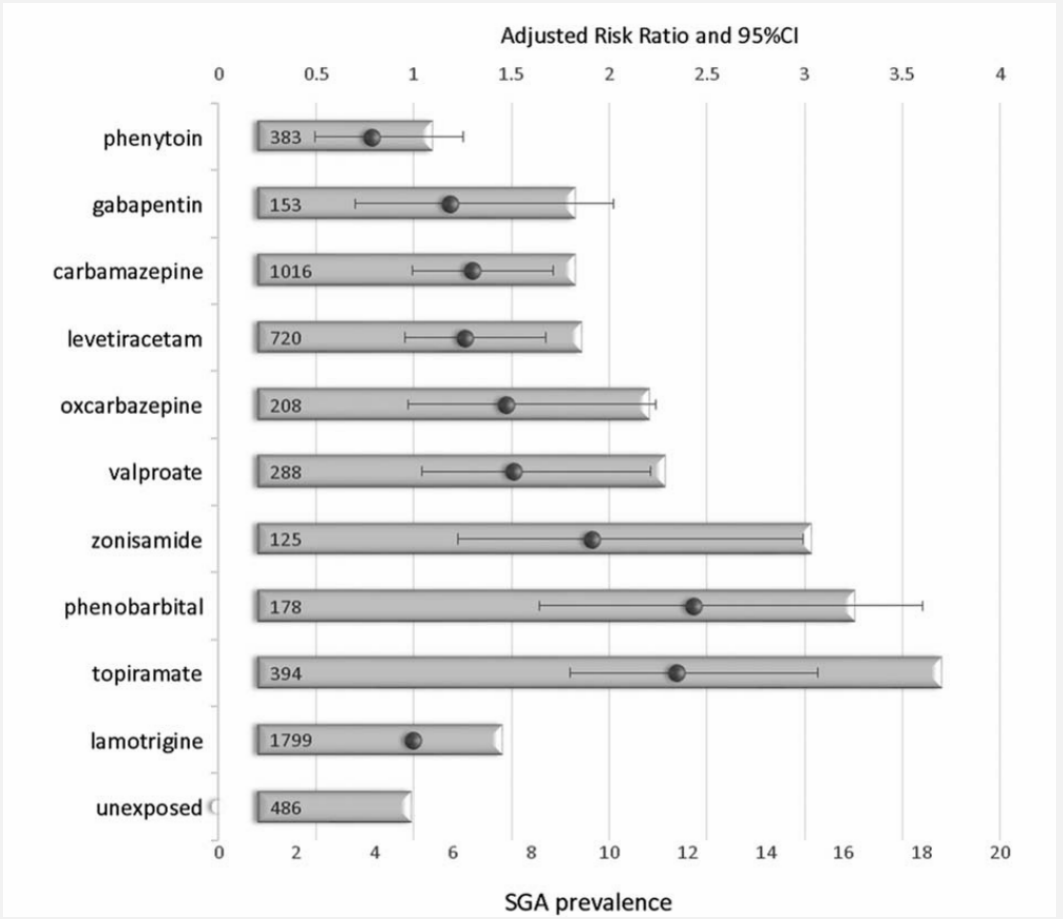
Table 3: **Association between prevalence of major congenital malformations and exposure to one of the four monotherapies in which a dose response was detectable**

ASM, antiseizure medication.

Tomson T, et al. *Lancet Neurol.* 2018;17:530–538.

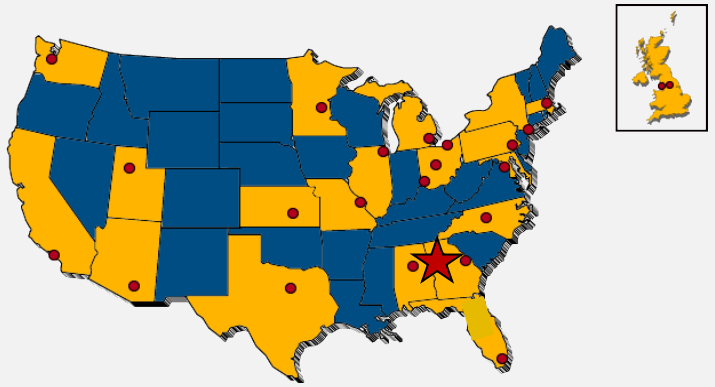
Neonatal Outcomes

Small gestational age



Hernandez-Diaz et al. *Ann Neurol.* 2017;82:457–465. 2. Pennel PB et al. *Epilepsy Behav.* 2012;24:449–456.

NEAD (Neurodevelopmental Effects of Antiepileptic Drugs)



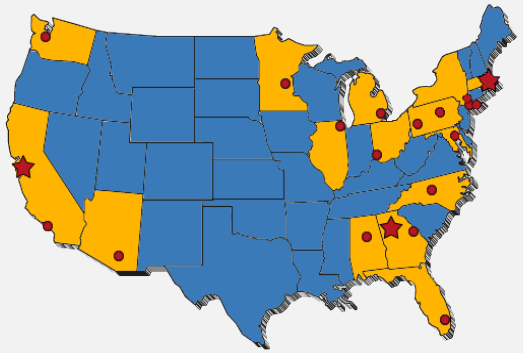
- Multicenter prospective, parallel-group observational study with statistical control
- 309 mother/child pairs, enrolled from late 1999 to early 2004, from 25 centers in USA & UK
- Antiepileptic drug (AED) monotherapy:
  - Carbamazepine (CBZ)
  - Lamotrigine (LTG)
  - Phenytoin (PHT)
  - Valproate (VPA)
- Blinded cognitive assessments: 2, 3, 4.5, & 6 years old
- Primary outcome: IQ at 6 years old

*NIH/NINDS #2RO1 NS 38455, NIH/NINDS #1 R01050659, UK Epilepsy Research Foundation #RB219738. IQ, intelligence quotient.
Meador KJ et al. NEJM 2009;360:1597–1605. Meador KJ et al. Lancet Neurol. 2013;12:244–52.

Maternal Outcomes & Neurodevelopmental Effects of Anti-Epileptic Drugs

MONEAD

Prospective, observational study, across 20 clinical sites



Multiple-PIs:
Kimford Meador, MD (Stanford)
Page B. Pennell, MD (University of Pittsburgh)

Obstetrics Core:
T. McElrath (BWH), M. Druzin (Stanford)

Neonatal Core: L. Van Marter (BWH) Semiology Core: J. French (NYU)
Mood Core: Z. Stowe (U Wisconsin)
OK Core: A. Birnbaum (U Minnesota)

Pregnant Women with Epilepsy (n=355), compared to 2 control groups:

Pregnant healthy controls (n=105)
Non-pregnant WWE (n=109)

Maternal Outcomes

- Seizures, OB complications, Depression

Children Outcomes

- Neurodevelopment, Neonatal complications, Breastfeeding

With PK modeling for level of exposure

Funded by NIH/NINDS,NICHD #U01-NS038455

Fetal Exposure to Valproate Associated With Lower IQ at Age 6

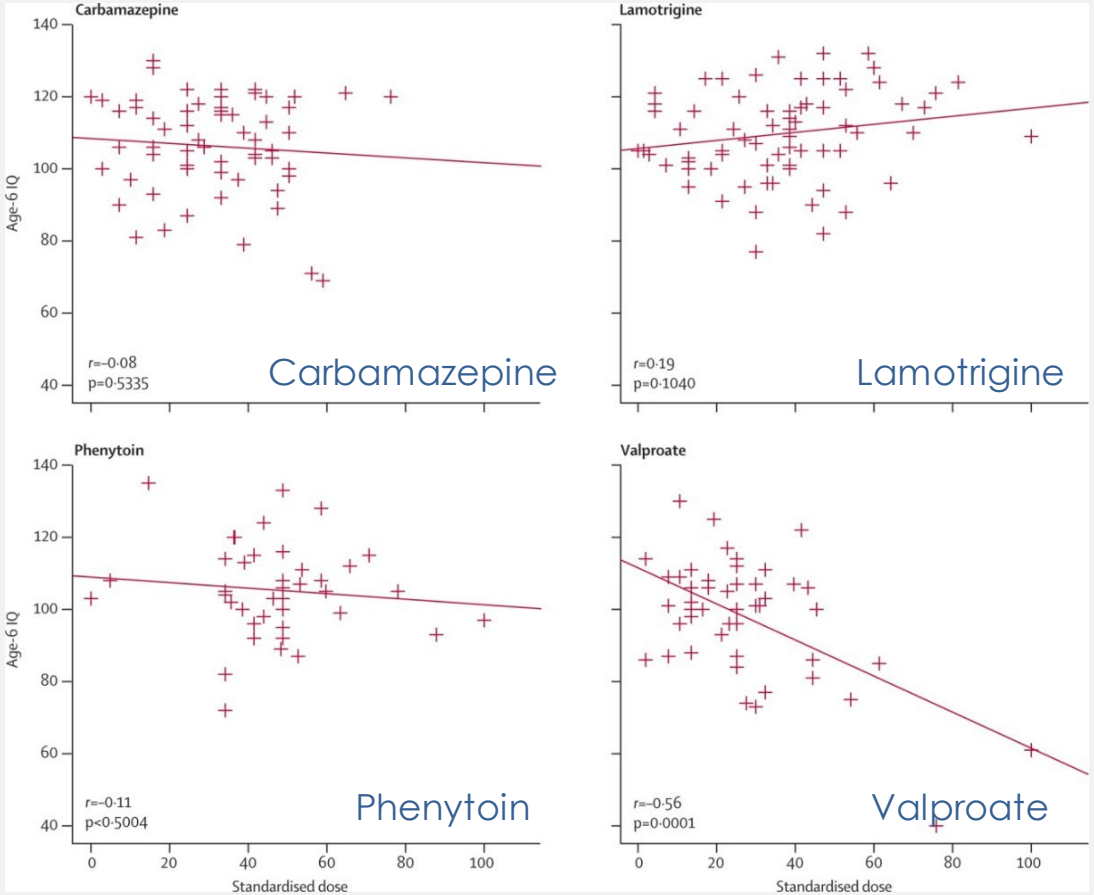
Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age and folate

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total-enrolled				
Participants	94 (30%)	100 (32%)	55 (18%)	62 (20%)
Mean IQ*	105 (102–108)	108 (105–110)	108 (104–112)	97 (94–101)
Difference	7 (3–12)	10 (6–15)	10 (5–16)	NA
p value†	0·0015	0·0003	0·0006	NA
Age-6-completers				
Participants	61 (27%)	74 (33%)	40 (18%)	49 (22%)
Mean IQ*	106 (103–109)	108 (105–111)	109 (105–113)	98 (95–102)
Difference	8 (3–13)	10 (6–15)	11 (5–16)	NA
p value†	0·0010	0·0003	0·0004	NA

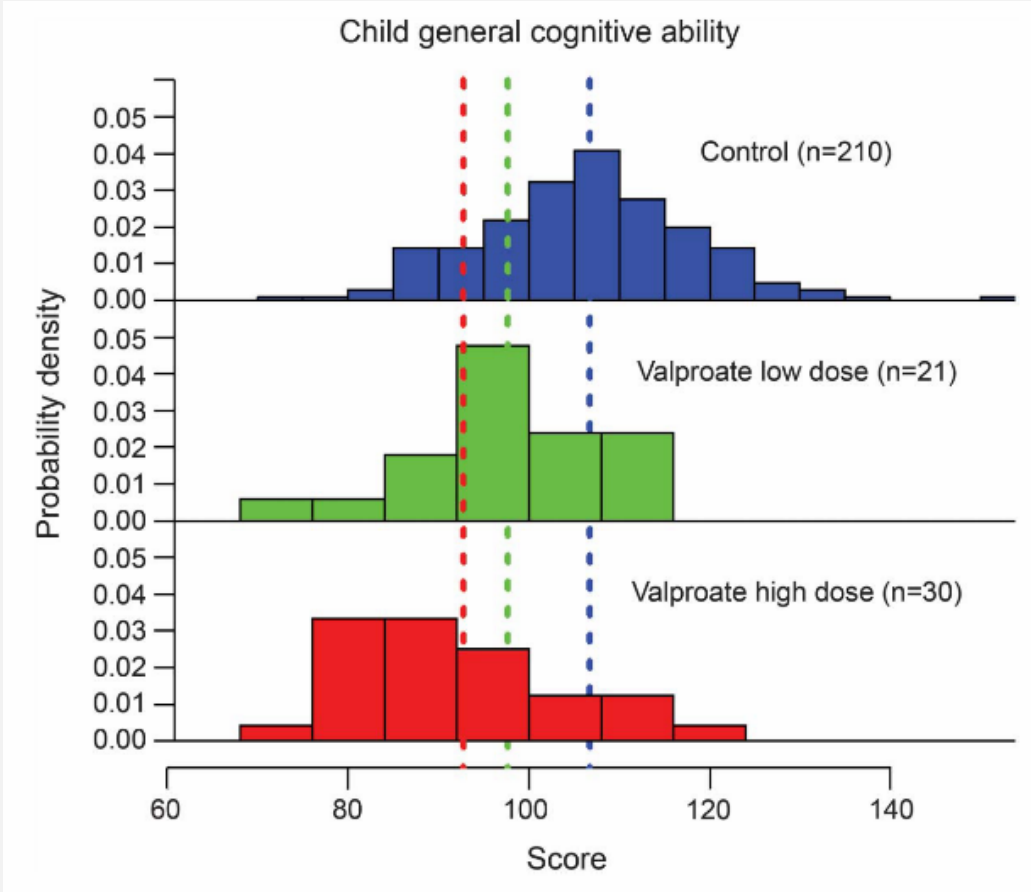
Meador KJ, et al. *Lancet Neurol*. 2013;12:244–252.

Dose-dependent IQ differences among VPA-exposed subject groups

NEAD study[1]



LMNDG study[2]



Colored dashed lines represent the mean IQ for each group.

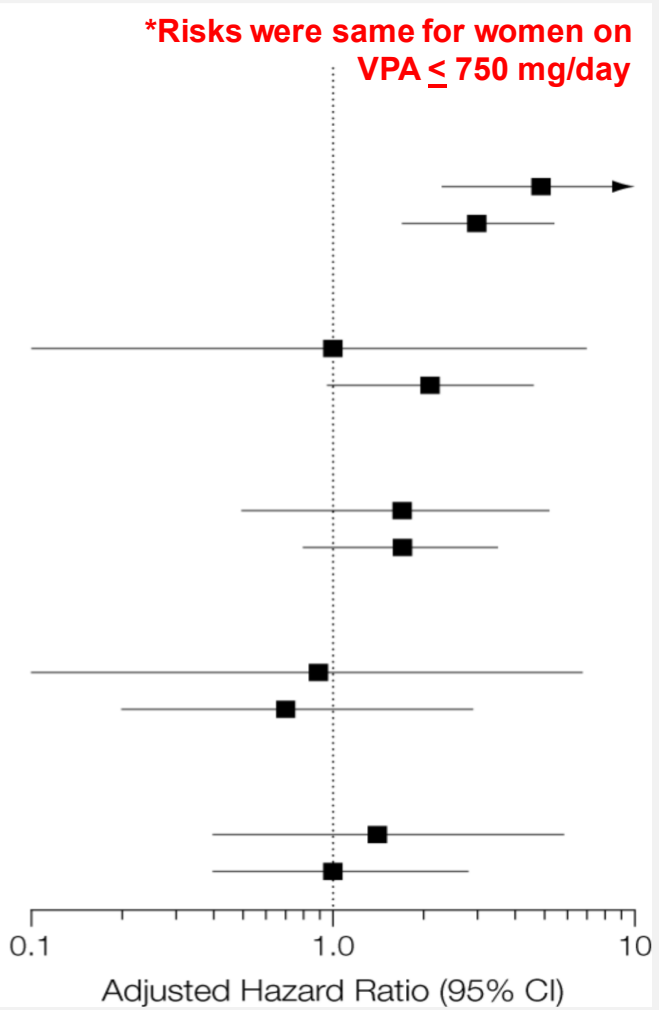
NEAD, Neurodevelopmental Effects of Antiepileptic Drugs. LMNDG, Neurodevelopmental Group
Meador KJ et al. Lancet Neurol 2013;12:244–52

Liverpool and Manchester

Baker G et al. Neurology 2015;84(4):382–390

Risk of autism with AED monotherapy

	No.		Adjusted Hazard Ratio (95% CI)
	Unexposed	Exposed	
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)



AED, antiepileptic drugs; VPA, valproic acid.
Christensen J, et al. JAMA. 2013;309(16):1696–1703.

Fetal exposure to levetiracetam is not associated with a negative neurodevelopmental effect

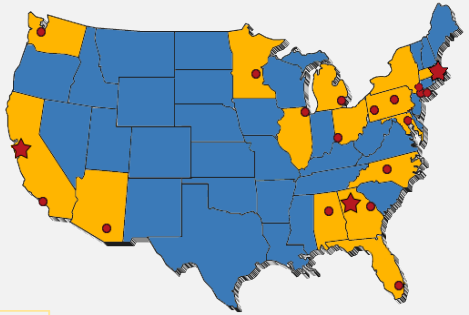
- Neuropsychological assessments were conducted between 5 and 9 years of age
- Adverse cognitive outcomes were not associated with increasing doses of LEV and TPM

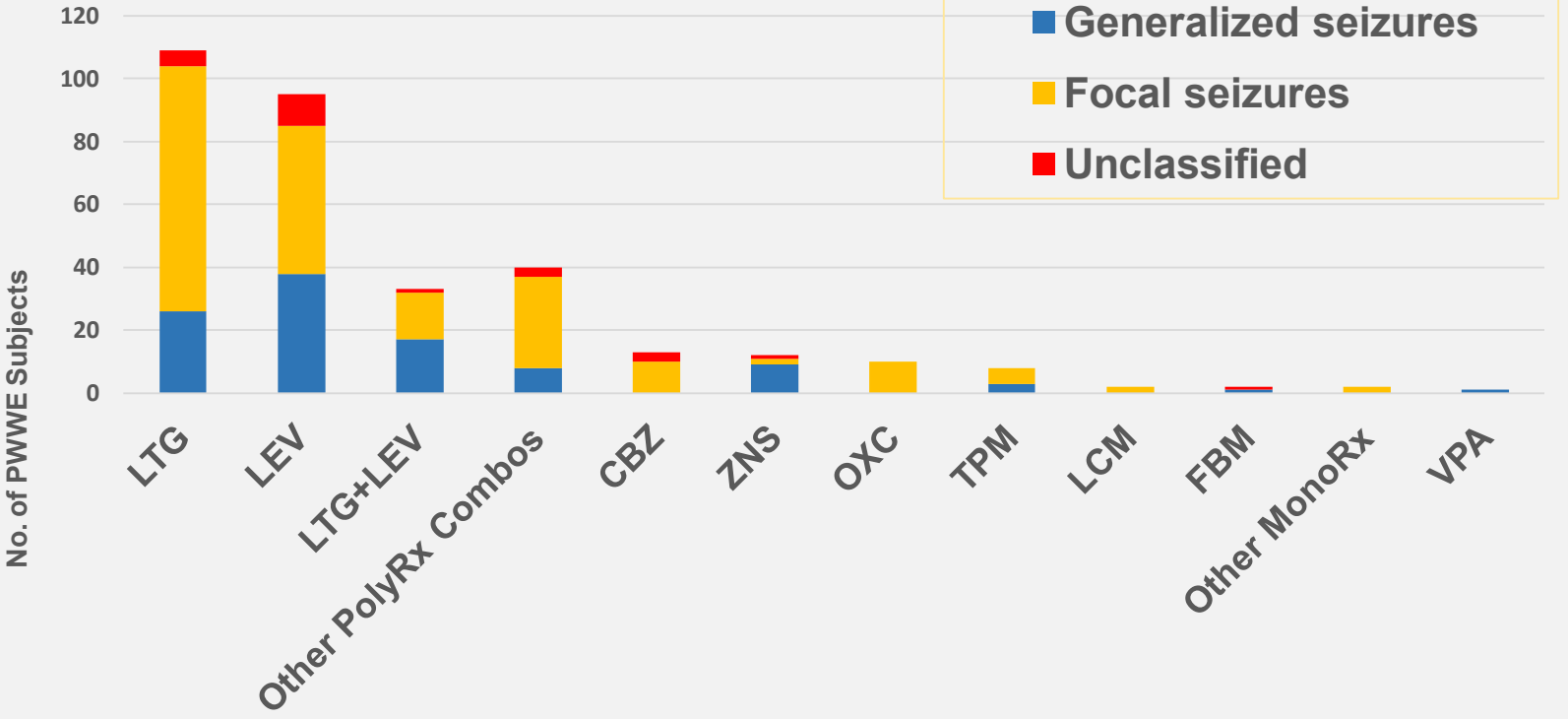
Table 2 Unadjusted means, standard errors, and rates below average performance by group for primary cognitive outcomes

	No medication (n = 55)		Gabapentin (n = 14)		Topiramate (n = 27)		Levetiracetam (n = 42)		Valproate (n = 47)	
WISC/WPPSI	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85
Full-scale IQ	99.7 (13.6)	3 (6)	103.6 (12.9)	1 (8)	100.5 (13.2)	3 (12)	99.0 (13.6)	5 (12)	95.9 (14.1)	9 (19)
Verbal abilities	101.7 (13.0)	4 (7)	105.0 (12.6)	1 (7)	99.2 (11.2)	3 (11)	101.0 (11.2)	1 (2)	93.7 (14.6)	10 (21)
Nonverbal abilities	100.8 (14.6)	6 (11)	104.3 (14.2)	1 (7)	102.4 (14.7)	3 (11)	99.6 (13.8)	7 (17)	101.5 (14.7)	6 (13)
Processing speed	97.1 (12.5)	8 (15)	103.6 (9.7)	0 (0)	100.0 (13.3)	3 (11)	94.7 (12.6)	7 (17)	94.6 (11.9)	8 (17)

LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, valproate; DCI, confidence intervals for difference from VPA.
Bromley RL et al. Neurology. 2016;87(18):1943–1953.

Prescribing Patterns in PWWE at MONEAD sites





Meador KJ, Pennell PB, May RC, Gerard E, Kalayjian L, Velez-Ruiz N, Penovich P, Cavitt J, French J, Hwang S, Pack A, Sam M, Moore E, Ippolito DM, MONEAD Investigator Group. *Epilepsy & Behavior* 2018.

JAMA Neurology | Original Investigation

Two-Year-Old Cognitive Outcomes in Children of Pregnant Women With Epilepsy in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study

Kimford J. Meador, MD; Morris J. Cohen, EdD; David W. Loring, PhD; Ryan C. May, PhD; Carrie Brown, MS; Chelsea P. Robalino, MStat; Abigail G. Matthews, PhD; Laura A. Kalayjian, MD; Elizabeth E. Gerard, MD; Evan R. Gedzelma
Alison M. Pack, M
and Neurodevelo

Findings This multicenter cohort study found no differences in 2-year-old children of women with epilepsy vs healthy women on the primary outcome of language domain scores of the Bayley Scales of Infant and Toddler Development, Third Edition. However, secondary analyses revealed that higher ASM levels and doses in the third trimester were associated with lower scores for other domains.

Meaning Overall, in this study, outcomes at 2 years of age did not differ by ASM exposures.

JAMA Neurol. doi:10.1001/jamaneurol.2021.1583
Published online June 7, 2021.

Higher ASM levels in the third trimester were associated with lower scores for the motor domain

BSID-III domain	No. of children[a]	Unadjusted analysis[b]		Adjusted analysis[c]	
		Parameter estimate (95% CI)	*P* value	Parameter estimate (95% CI)	*P* value
Maximum ratio of ABL[d]					
Language	258	−10.3 (−16.2 to −4.3)	<.001	−4.2 (−10.5 to 2.2)	.20
Motor	256	−7.9 (−12.2 to −3.7)	<.001	−5.6 (−10.7 to −0.5)	.03
Cognitive	261	−6.5 (−11.0 to −1.9)	.005	−2.8 (−7.9 to 2.3)	.28
Social-emotional	261	−4.9 (−10.6 to 0.7)	.09	−0.4 (−6.9 to 6.1)	.90
General adaptive	259	−8.8 (−14.0 to −3.5)	.001	−6.1 (−12.3 to 0.05)	.052
Maximum ratio of DDD[e]					
Language	270	−1.9 (−3.2 to −0.7)	.003	−0.3 (−1.7 to 1.0)	.62
Motor	267	−1.1 (−2.0 to −0.2)	.03	−0.1 (−1.2 to 1.0)	.87
Cognitive	274	−1.8 (−2.8 to −0.8)	<.001	−0.9 (−2.0 to 0.3)	.14
Social-emotional	272	−1.4 (−2.6 to −0.2)	.03	−0.5 (−2.0 to 0.9)	.49
General adaptive	270	−2.1 (−3.2 to −1.0)	<.001	−1.4 (−2.8 to −0.05)	.049

Higher ASM doses in the third trimester were associated with lower scores in the general adaptive domain

Other important recent neurodevelopmental studies

JAMA Neurology | Original Investigation

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD, PhD; Jakob Christensen, MD, PhD

IMPORTANCE Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

OBJECTIVE To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

DESIGN, SETTING, AND PARTICIPANTS The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden (1996-2017; analysis performed February 2022). From 4 702 774 alive-born children with available mother-child identities and maternal prescription data, this study included 4 494 926 participants. Children from a multiple pregnancy or with chromosomal disorders or uncertain pregnancy length were excluded (n = 207 848).

EXPOSURES Prenatal exposure to ASM determined from maternal prescription fills between last menstrual period and birth.

MAIN OUTCOMES AND MEASURES We estimated cumulative incidence at age 8 years in exposed and unexposed children. Cox regression adjusted for potential confounders yielded adjusted hazard ratios (aHRs) with 95% CIs for autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder (ASD and/or ID).

RESULTS A total of 4 494 926 children were included; 2 306 993 (51.3%) were male, and the median (IQR) age at end of follow-up was 8 (4.0-12.1) years. Among 21 634 unexposed children of mothers with epilepsy, 1.5% had a diagnosis of ASD and 0.8% (numerators were not available because of personal data regulations in Denmark) of ID by age 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD, and 3.1% and 2.4% had ID. The aHRs for ASD and ID after topiramate exposure were 2.8 (95% CI, 1.4-5.7) and 3.5 (95% CI, 1.4-8.6), respectively, and after valproate exposure were 2.4 (95% CI, 1.7-3.3) and 2.5 (95% CI, 1.7-3.7). The aHRs were elevated with higher ASM doses compared with children from the general population. The duotherapies levetiracetam with carbamazepine and lamotrigine with topiramate were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy: levetiracetam with carbamazepine: 8-year cumulative incidence, 5.7%; aHR, 3.5; 95% CI, 1.5-8.2; lamotrigine with topiramate: 8-year cumulative incidence, 7.5%; aHR, 2.4; 95% CI, 1.1-4.9. No increased risk was associated with levetiracetam with lamotrigine (8-year cumulative incidence, 1.6%; aHR, 0.9; 95% CI, 0.3-2.5). No consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepin, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital.

CONCLUSIONS AND RELEVANCE In this cohort study, prenatal exposure to topiramate, valproate, and several duotherapies were associated with increased risks of neurodevelopmental disorders.

Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Topiramate has significant negative neurodevelopmental effects

Seizure: European Journal of Epilepsy 105 (2023) 56–64

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Adaptive behaviour in children exposed to topiramate in the womb: An observational cohort study

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[b] Greater Manchester Mental Health NHS Foundation Trust, UK
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[d] Division of Neuroscience and Experimental Psychology Science, The University of Manchester, UK
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ARTICLE INFO

Keywords:
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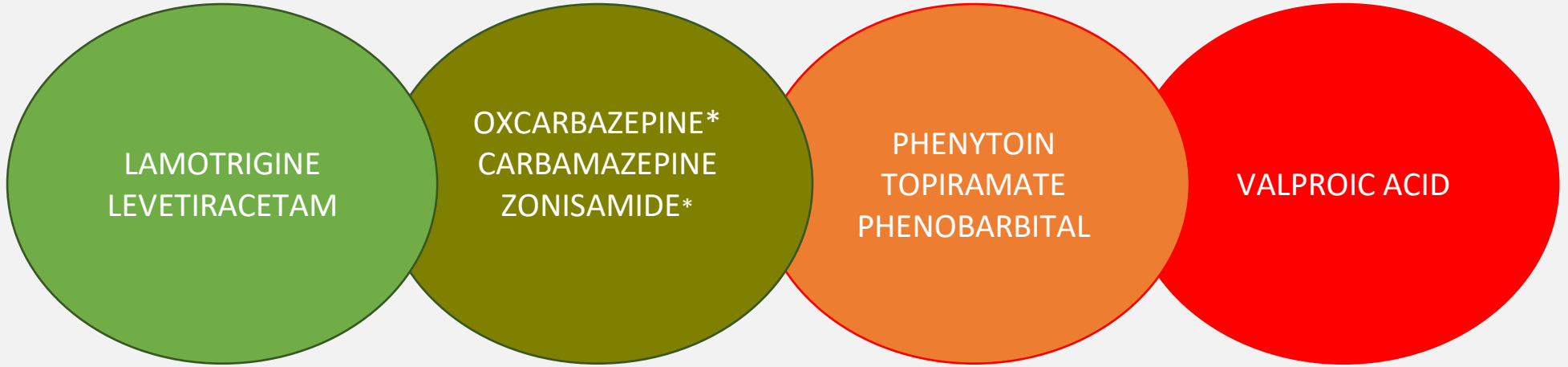
Antiseizure medications
Epilepsy
Topiramate
Pregnancy
Autism

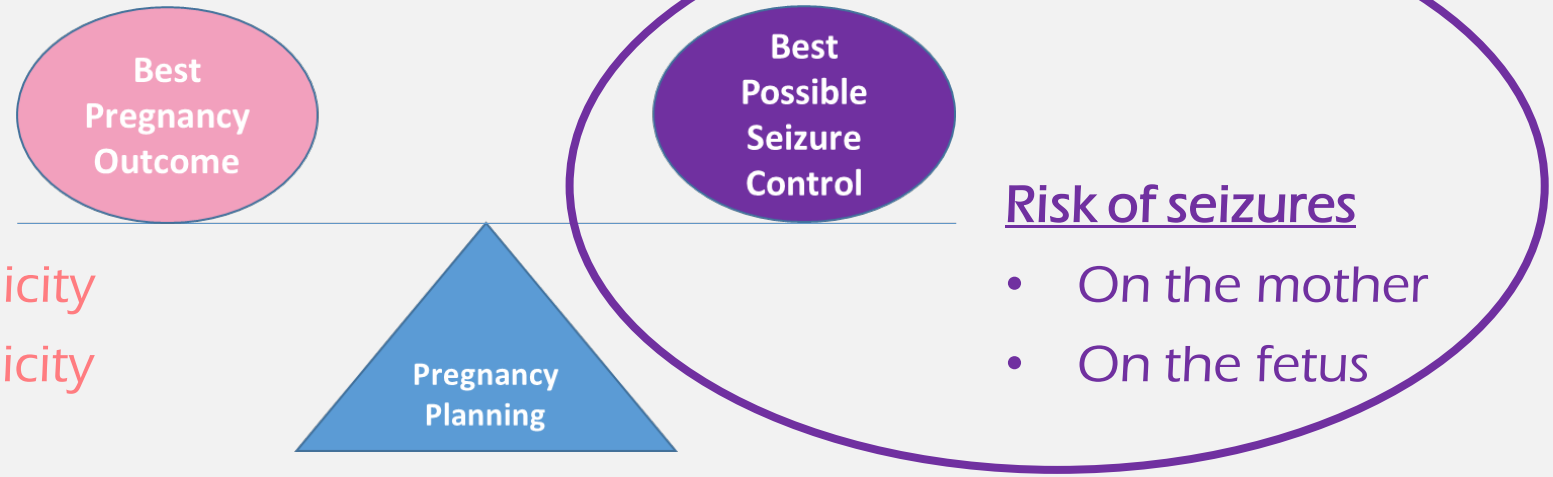
ABSTRACT

Objective: Many women with epilepsy need to continue anti-seizure medications (ASMs) throughout pregnancy. The current study investigated adaptive behaviour outcomes in children exposed to topiramate in the womb.
Method: An observational, cross-sectional study was designed, recruiting mother-child-pairs from the UK Epilepsy and Pregnancy Register (UKEPR). Health, developmental histories and Vineland Adaptive Behaviour Scale-Third Edition (VABS-III) assessments were administered via telephone by a blinded researcher, supplemented with prospectively collected pregnancy and medication information. Topiramate monotherapy exposed children were compared to VABS-III normative data as recruitment was disrupted by the COVID-19 pandemic.
Results: Thirty-four women with epilepsy from 135 (25%) initially agreed to participate in the study, of whom 26 women completed telephone interviews about their children ($n = 28$). Children ranged from 2.5 to 17 years of age at the time of assessment. Six topiramate-exposed children were born small for gestational age, and there were significant associations between birthweight, dose and VABS-III scores. Significantly lower scores were observed in topiramate-exposed children ($n = 21$) with a significant dose-response relationship established after adjustment for parental educational level. Daily mean dosage was 280.21 mg, with high dosages of topiramate associated with a 12-point reduction in VABS-III scores. Additionally, four topiramate-exposed children (19.05%) had diagnoses of Autism Spectrum Disorder, which was significantly higher than UK prevalence rates (1.1%).
Conclusions: The findings of poorer adaptive behaviour, higher incidence of ASD and associations with birth weight are of concern and require further validation and replication using larger prospectively-recruited samples and comparator cohorts. Implications for research and clinical practice are discussed.

My Current Preferential selection of AEDs for WWE of childbearing age



Personalized equation: Benefits versus risks of ASM during pregnancy



Risk of medications

- Structural teratogenicity
- Cognitive teratogenicity
- Neonatal outcomes

Risk of seizures

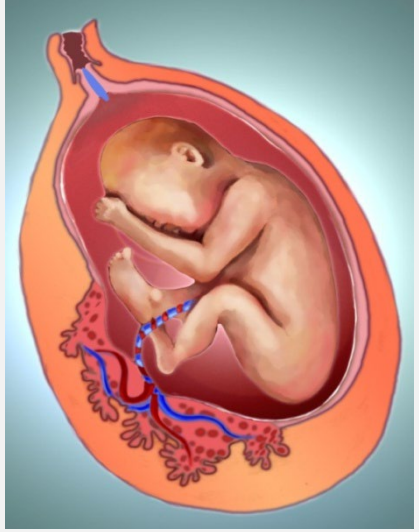
- On the mother
- On the fetus

Risk of attempting to optimize the ASM regimen

- Seizure control
- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

Risk of Seizures



Generalized Tonic-Clonic Convulsions

- Maternal & fetal hypoxia & acidosis, fetal brady
- Miscarriage & stillbirths
- Developmental delay (≥5 GTCC in pregnancy)

All seizures:

- Increased OR for LBW, SGA, preterm delivery **(1.3-1.6 fold)**

Status epilepticus

- 30% maternal mortality; 50% infant mortality

Maternal Risks

- Death rate during pregnancy in WWE 10-fold higher (SUDEP)
- 11.5 OR [95% CI, 8.64-15.19]), of death during delivery hospitalization

Teramo K, et al. *J Perinat Med*. 1979;7(1):3-6; Vinten J, et al. *Neurology* 2005;64(6):949-54; Chen YH, et al. *Arch Neurol* 2009;66(8):979-84; Macdonald SC, et al. JAMA Neurol 2015.

Original Investigation

Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States

Sarah C. MacDonald, BSc; Brian T. Bateman, MD, MSc; Thomas F. McElrath, MD, PhD; Sonia Hernández-Díaz, MD, DrPH

IMPORTANCE Between 0.3% and 0.5% of all pregnancies occur among women with epilepsy. Evidence suggests an increase in perinatal morbidity and mortality among women with epilepsy. However, these risks have not been quantified in large population-based samples.

OBJECTIVE To report on the risk for death and adverse outcomes at the time of delivery for women with epilepsy in the United States.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of pregnant women identified through delivery hospitalization records from the 2007-2011 Nationwide Inpatient Sample. From this representative sample of 20% of all US hospitals, we obtained a weighted sample of delivery hospitalizations from 69 385 women with epilepsy and 20 449 532 women without epilepsy.

MAIN OUTCOMES AND MEASURES Obstetrical outcomes including maternal death, cesarean delivery, length of stay, preeclampsia, preterm labor, and stillbirth.

RESULTS Women with epilepsy had a risk of death during delivery hospitalization of 80 deaths per 100 000 pregnancies, significantly higher than the 6 deaths per 100 000 pregnancies found among women without epilepsy (adjusted odds ratio [OR], 11.46 [95% CI, 8.64-15.19]). Women with epilepsy were also at a heightened risk for other adverse outcomes, including preeclampsia (adjusted OR, 1.59 [95% CI, 1.54-1.63]), preterm labor (adjusted OR, 1.54 [95% CI, 1.50-1.57]), and stillbirth (adjusted OR, 1.27 [95% CI, 1.17-1.38]), and had increased health care utilization, including an increased risk of cesarean delivery (adjusted OR, 1.40 [95% CI, 1.38-1.42]) and prolonged length of hospital stay (>6 days) among both women with cesarean deliveries (adjusted OR, 2.13 [95% CI, 2.03-2.23]) and women with vaginal deliveries (adjusted OR, 2.60 [95% CI, 2.41-2.80]).

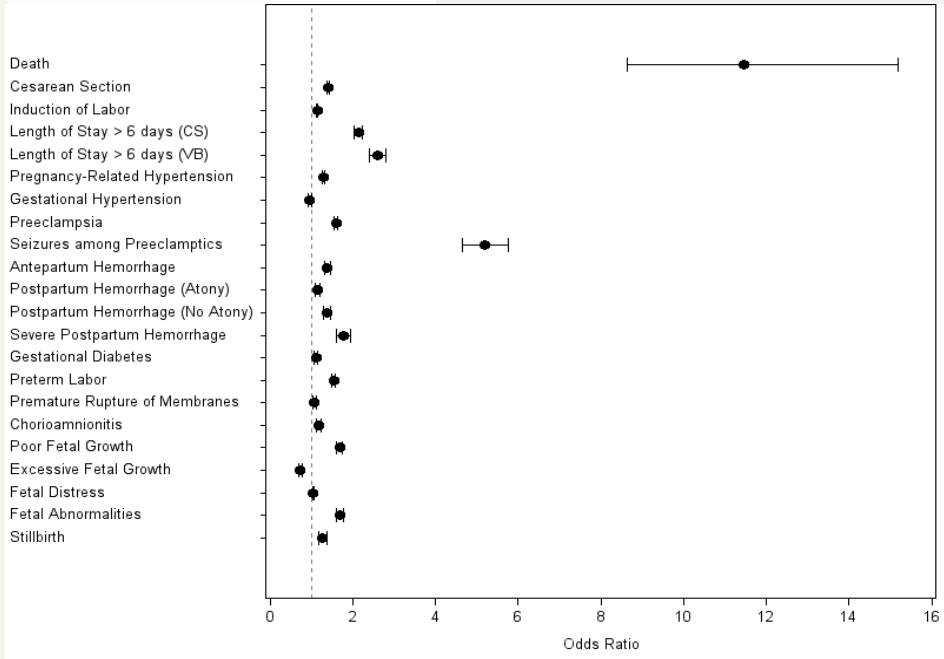
CONCLUSIONS AND RELEVANCE Findings suggest that women with epilepsy are at considerably heightened risk for many adverse outcomes during their delivery hospitalization, including a more than 10-fold increased risk of death, and that increased clinical attention is imperative for these pregnancies.

Editorial page 973

Author Audio Interview at jamaneurology.com

Supplemental content at jamaneurology.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 1084



Original Article

The Obstetrical Care and Delivery Experience of Women with Epilepsy in the MONEAD Study

Thomas F. McElrath, MD, PhD[1] Maurice Druzin, MD[2] Linda J. Van Marter, MD[3] Ryan C. May, PhD[4] Carrie Brown, MS[4] Alice Stek, MD[5] William Grobman, MD[6] Mary Dolan, MD[7] Patricia Chang, MD[8] Kellie Flood-Schaffer, MD[9] Lamar Parker, MD[10] Kimford J. Meador, MD[12] Page B. Pennell, MD[11] and for the MONEAD Investigator Group

Objective We examined mode of delivery among pregnant women with epilepsy (PWWE) versus pregnant controls (PC). We hypothesize that PWWE are more likely to deliver by cesarean.

Study Design The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is an observational, prospective, multicenter investigation of pregnancy outcomes funded by the National Institute of Health (NIH). MONEAD enrolled patients from December 2012 through January 2016. PWWE were matched to PC in a case:control ratio of 3:1. This analysis had 80% power to detect a 36% increase in cesarean frequency assuming a baseline rate of 30% among PC at an $\alpha = 0.05$.

Results This report analyzed 331 PWWE (76%) and 102 PC (24%) who gave birth while enrolled in the study. PWWE and PC had similar rates of cesarean delivery (34.7 vs. 28.6%; $p = 0.27$). Of women with cesarean, rates of cesarean without labor were similar between groups for those delivering in recruitment hospitals (48.2 vs. 50.0%) but in nonrecruitment hospitals, cesarean rates without labor were over two-fold higher among PWWE than those of PC (68.8 vs. 30.8%; $p = 0.023$). Receipt of a cesarean after labor did not differ for PWWE compared to PC or by type of antiepileptic drug among the PWWE.

Conclusion These findings suggest that the obstetrical experiences of PWWE and PC are similar. An interesting deviation from this observation was the mode of delivery with higher unlabored cesarean rates occurring among PWWE in nonrecruitment hospitals. As the study recruitment hospitals were tertiary academic centers and nonrecruitment hospitals tended to be community-based institutions, differences in perinatal expertise might contribute to this difference.

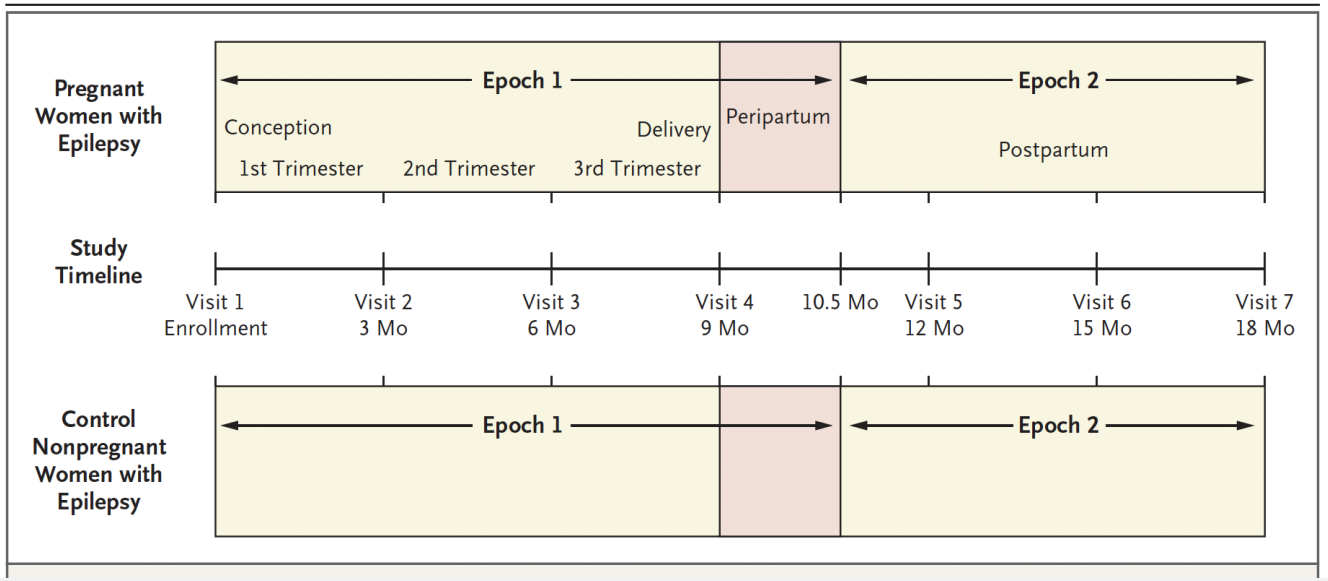
Key Points

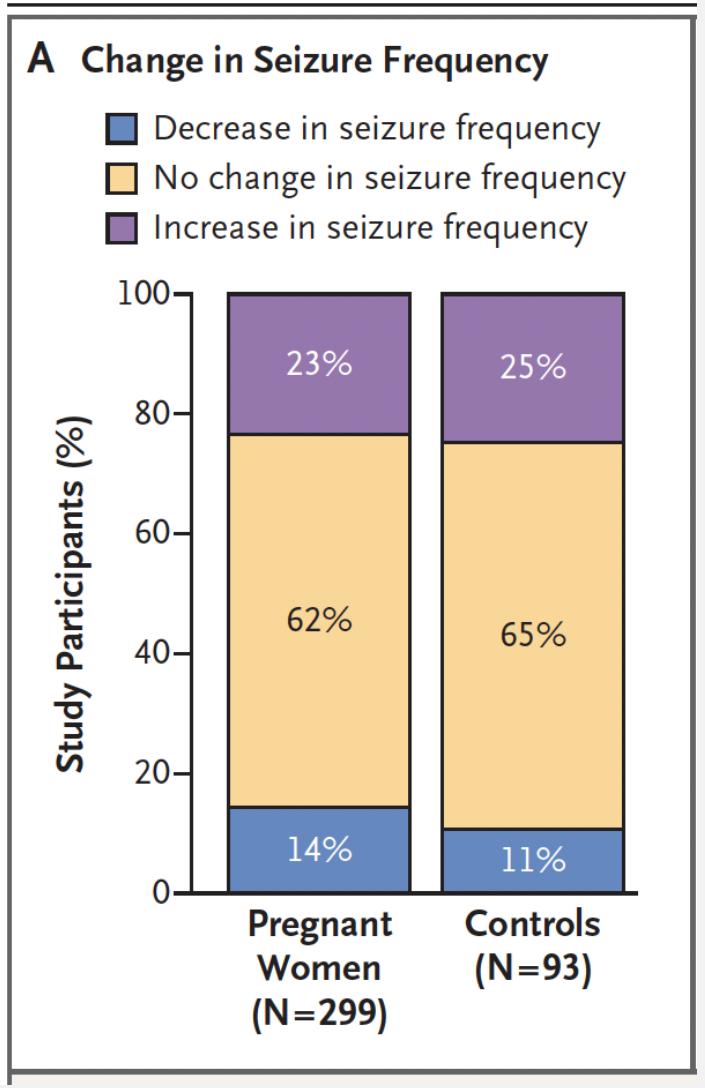
- Unlabored cesarean rates higher among women with epilepsy.
- Provider preference may influence delivery mode among women with epilepsy.
- Type and amount of antiepileptic drug was not associated with mode of delivery.

McElrath TF et al. *Am J Perinatol.* 2022 Dec 31. Epub ahead of print. PMID: 35253

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy

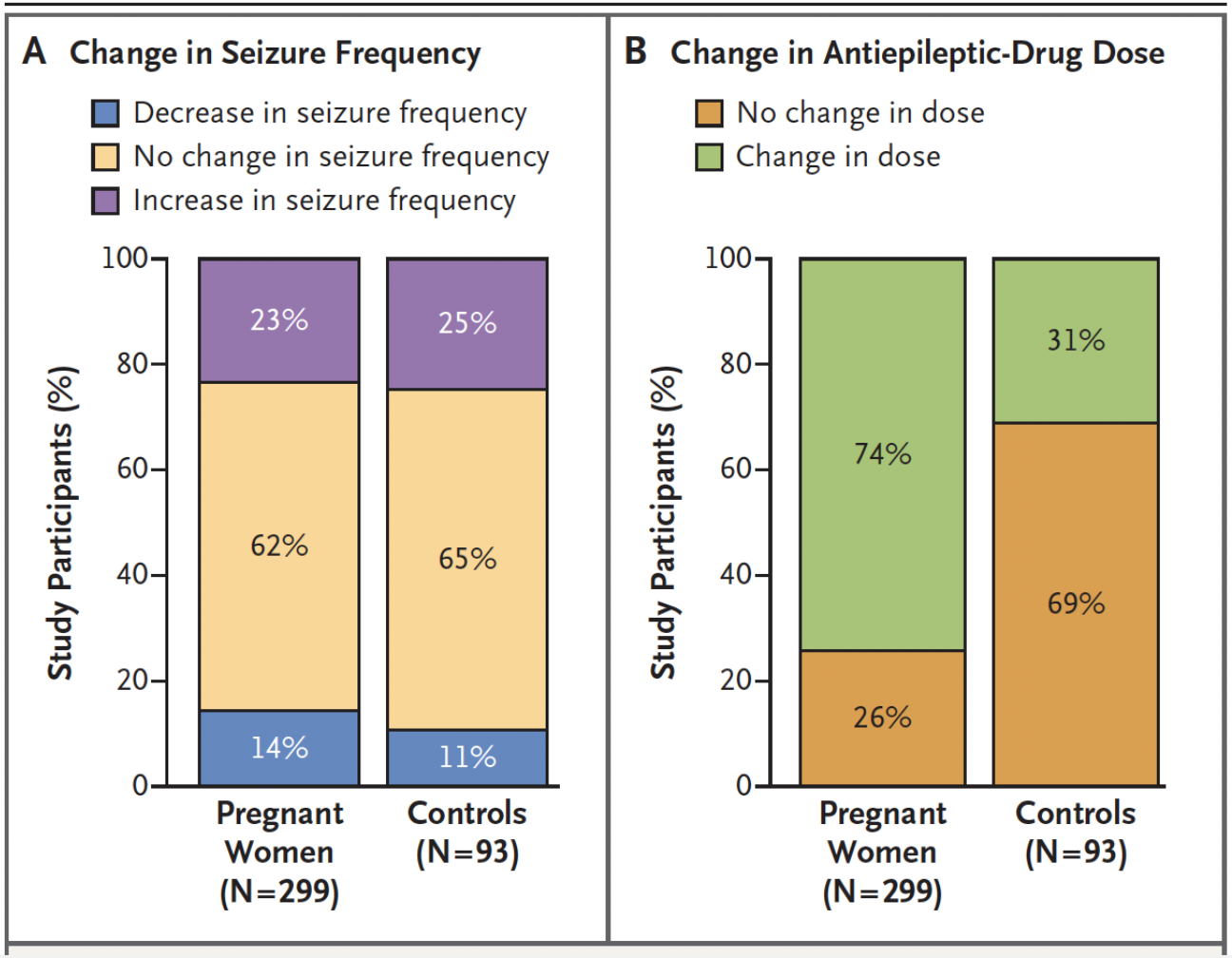
MONEAD Study Design for Seizure Outcomes





Pennell PB et al. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. *N Engl J Med.* 2020 Dec 24;383(26):2547-2556.

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy



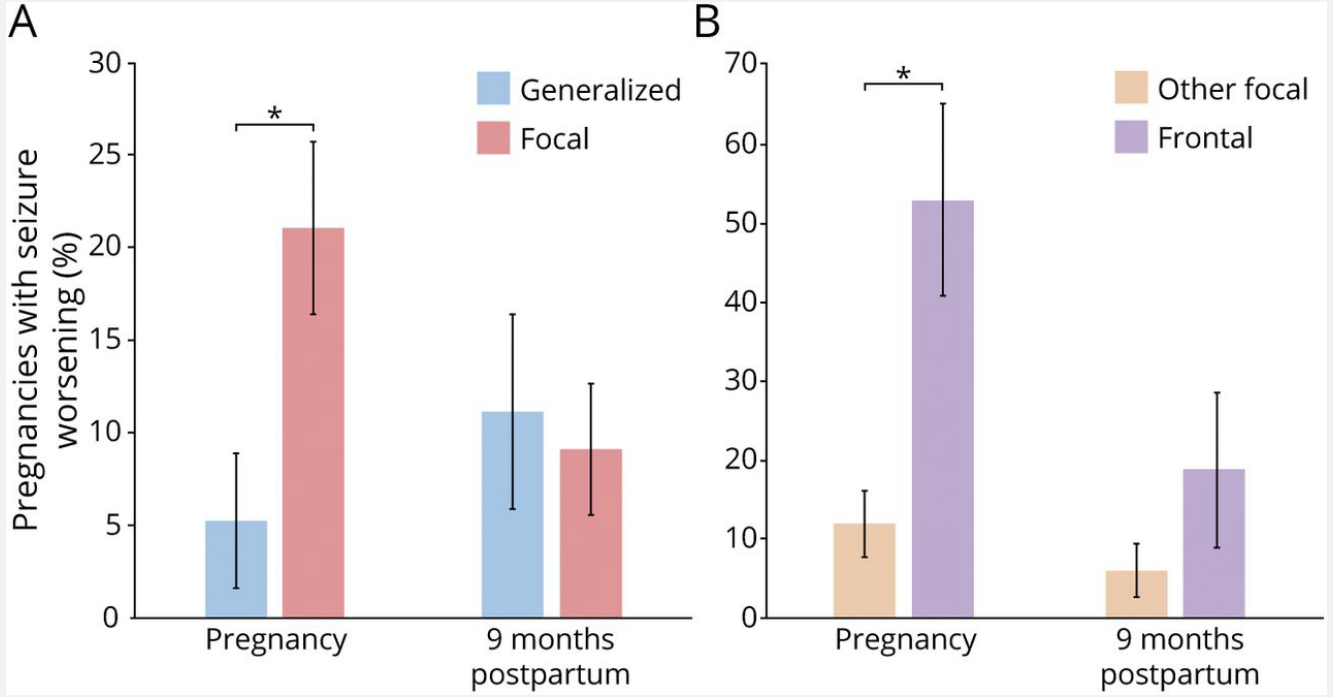
Pennell PB, French JA, May RC, et al. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Risk Factors for worsening of seizures with impaired awareness during pregnancy and peripartum

- Evaluated in 23% of PWWE with increased seizures with impaired awareness (incl. GTCS)
- No differences in seizure types, ASM regimen or type
- Sole risk factor was seizure freedom in 9 months prior to conception:
  - Adjusted OR = 0.26, 95% CI [0.14, 0.46], p<0.001).

Pennell PB, French JA, May RC, et al.. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Variations in Seizure Frequency during Pregnancy and Postpartum by Epilepsy Type



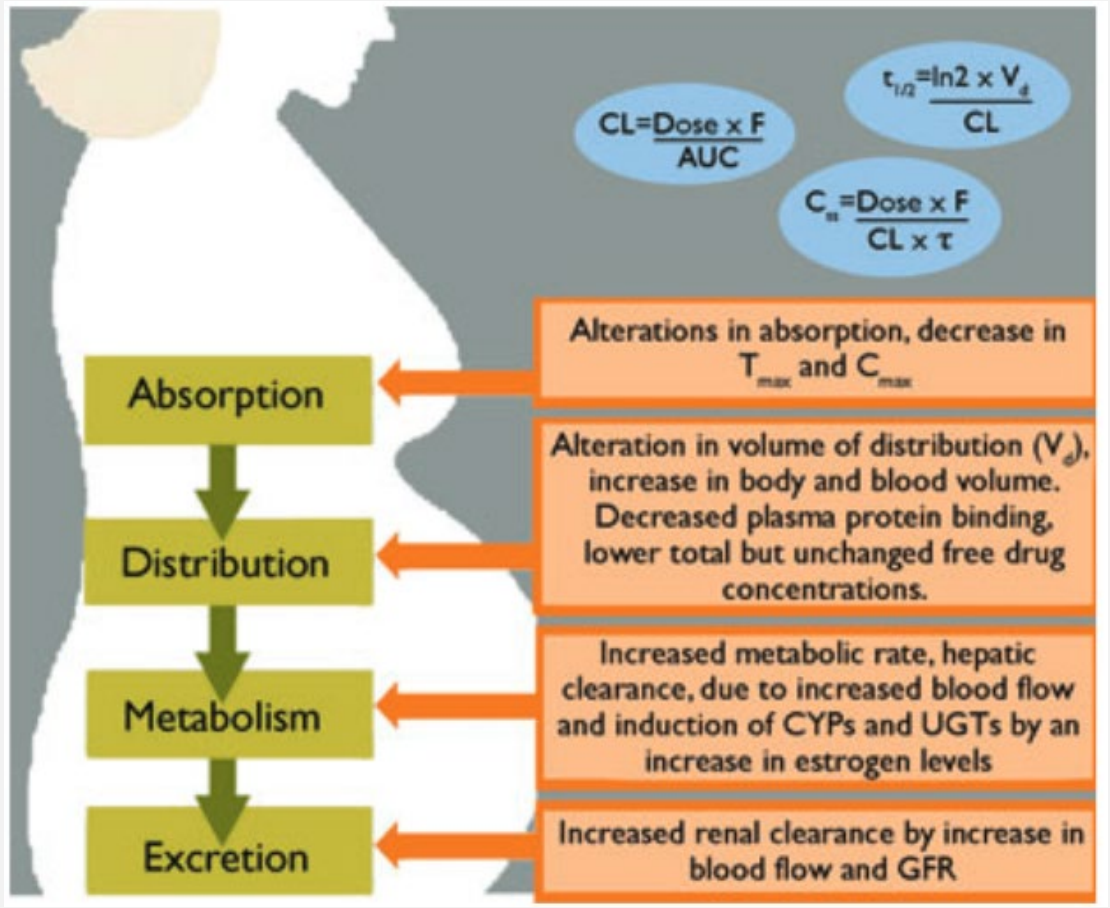
- 99 patients contributing 114 pregnancies
- **Increased** seizure frequency during pregnancies of women with :
  - ❖ **focal** vs generalized epilepsy: 21.1% vs 5.3%, **OR 4.70**; 95% CI (1.00, 22.00); p = 0.0497
  - ❖ **frontal** lobe vs other focal epilepsy: **OR 8.00**; 95 % CI (2.19, 29.21); p = 0.0017
  - ❖ **polytherapy** vs monotherapy: **OR = 8.36**, 95% CI = (2.07, 33.84), p = 0.0029 - regardless of the medication or epilepsy type
  - ❖ **Lack** vs presence of **preconception seizure freedom**: **OR = 6.418**; p = 0.0076

Voinescu PE et al. *Neurology* Feb 2022, 98 (8) e802-e807

PREGNANCY - POSTPARTUM

- Pharmacokinetic considerations

Pharmacokinetic changes in drug disposition during pregnancy



Tomson et al. *Epilepsia* 2013 ILAE

Direction of pharmacokinetic changes for antiseizure medications during pregnancy

ASM	Concentration	Clearance	Timing of Peak Clearance
Carbamazepine	No change	No change	N/A
Carbamazepine-Epoxide	No change	No change	N/A
Levetiracetam	Decrease	Increase	1st trimester
Lamotrigine	Decrease	Increase	3rd trimester
Phenytoin	Decrease	Increase	3rd trimester
Phenobarbital	Decrease	Increase	N/A
Oxcarbazepine	Decrease	Increase	2nd/3rd trimester
Topiramate	Decrease	Increase	2nd/3rd trimester
Valproate	Decrease	No change	N/A
Zonisamide	Decrease	Increase	3rd trimester

Lemley RL and Voinescu PE. Queenan's Management of High-Risk Pregnancy: An Evidence-Based Approach, 7th edition – Chapter 24

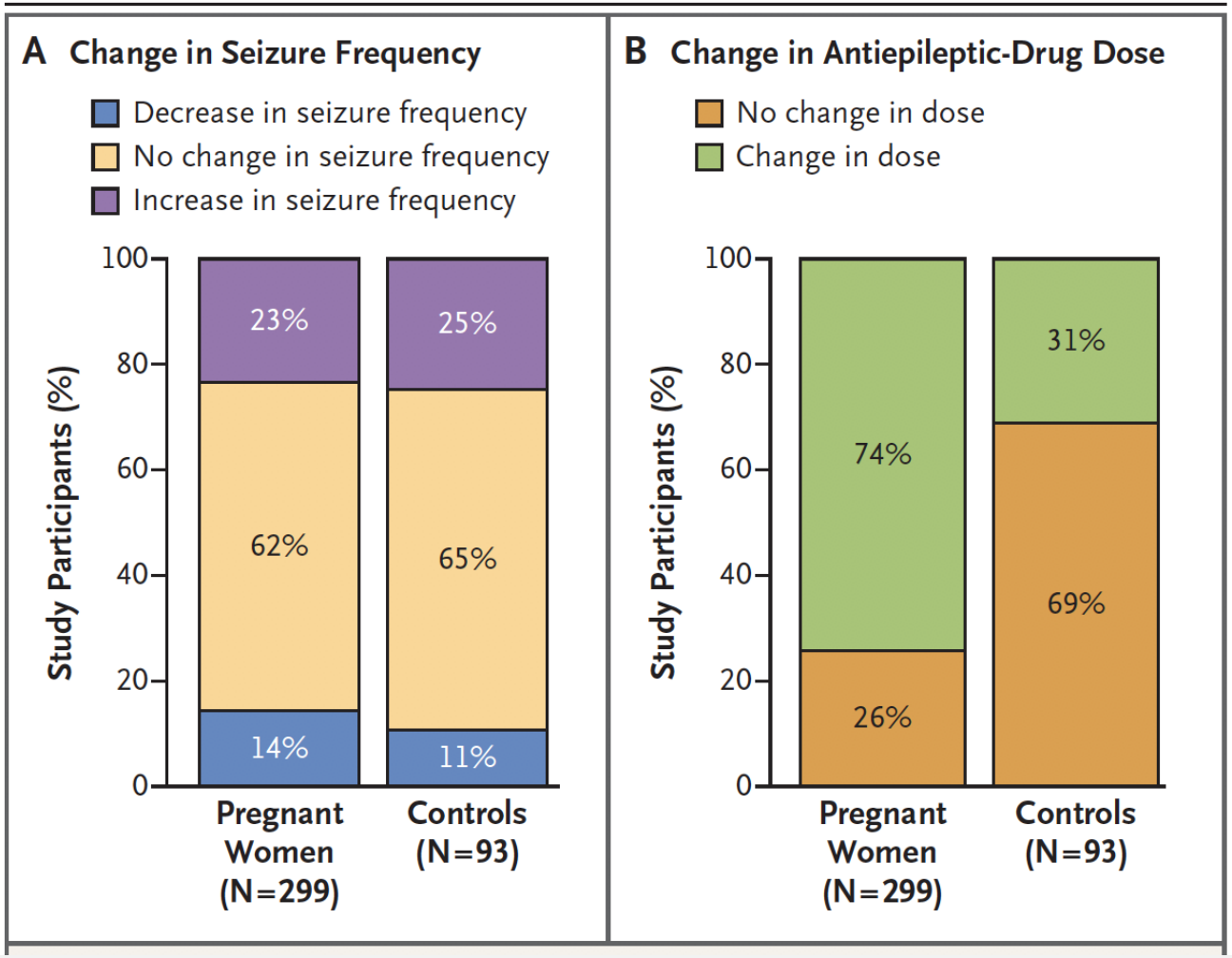
Summary of pharmacokinetic changes

- The magnitude and time course of pregnancy-related pharmacokinetic changes vary for different ASM[1-4]
- Dose adjustments are necessary to maintain a pre-conception target concentration[5]
- **A decrease by more than 35% of the preconception baseline is associated with a significant increase in seizure frequency**[1,3]
- Extended-release formulations and twice (or more times) per day dosing are preferred to minimize ASM level fluctuations

The Obstetrician is our partner in keeping seizures under control during pregnancy by helping with monthly blood drawns to check antiepileptic drug serum concentration (level)

1. Voinescu PE et al. Neurology 2018;91:e1228-e1236; 2. Johnson et al. Epilep Behav 2014;33:49–53; 3. Pennell et al. Neurology 2007;70(22 Pt 2):2130–6. 4. Pennell PB, et al. MONEAD Study Group. JAMA Neurol. 2022;79(4):370-379. 5. Pennell PB, et al. MONEAD Study Group. NEJM. 2020; 383(26):2547-2556

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy



Pennell PB, French JA, May RC, et al. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Suggestions for the management of pregnant women with epilepsy

- 1st TM: Re-dosing if vomiting within 1h, ensure they have Ob/MFM care
- 2nd TM: Detailed structural US
- 3rd TM: Peripartum and postpartum issues
  - Dose AEDs accurately and have the patient bring her medications to the hospital (same time/formulation)
  - Epidural anesthesia recommended to allow some periods of less than maximal intensity of physical stressors during labor and delivery
  - Lorazepam/IV AEDS should be available during labor and delivery as needed for acute seizure control
  - Do not neglect psychiatric needs

Voinescu PE and Pennell PB. *Semin Neurol* 2017

POSTPARTUM

- Seizure provoking factors
- Pharmacokinetic considerations
- Breastfeeding

Summary ASM exposure via breastmilk

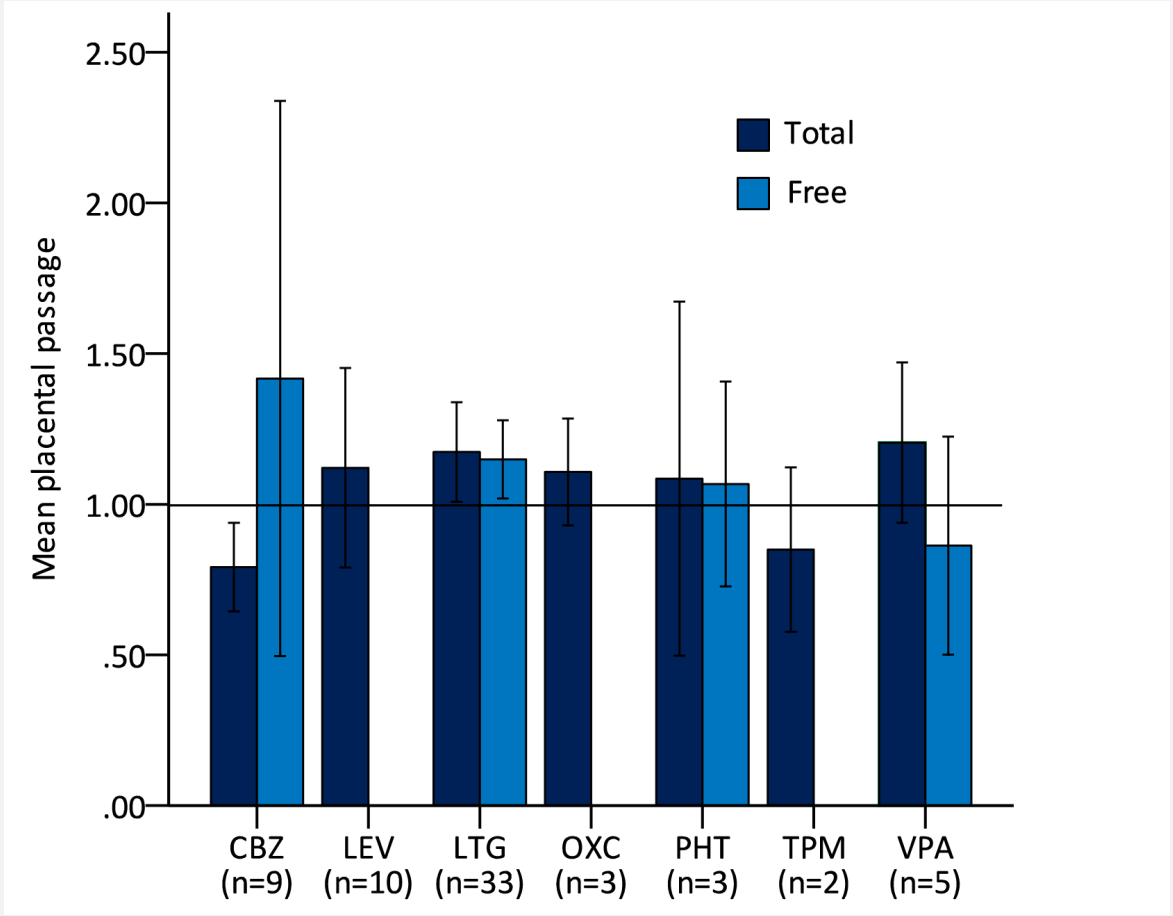
- The degree of penetration into breast milk varies for different ASMs
  - Some penetrate in potentially clinically important amounts: PRM, LEV, GBP, LTG, TPM
  - Others less so: VPA, PB, PHT, CBZ
- Significantly lower exposure than in utero (MONEAD data)

ASM, antiseizure medication; CBZ, carbamazepine; GBP, gabapentin; IQ, intelligence quotient; LEV, levetiracetam; LTG, lamotrigine; NEAD, neurodevelopmental effects of antiepileptic drugs; MONEAD, maternal outcomes and neurodevelopmental effects of antiepileptic drugs; PB, phenobarbital; PHT, phytoin; PRM, primidone; TPM, topiramate; VPA, valproic acid.

Meador, et al. JAMA Pediatr. 2014;168(8):729–736.

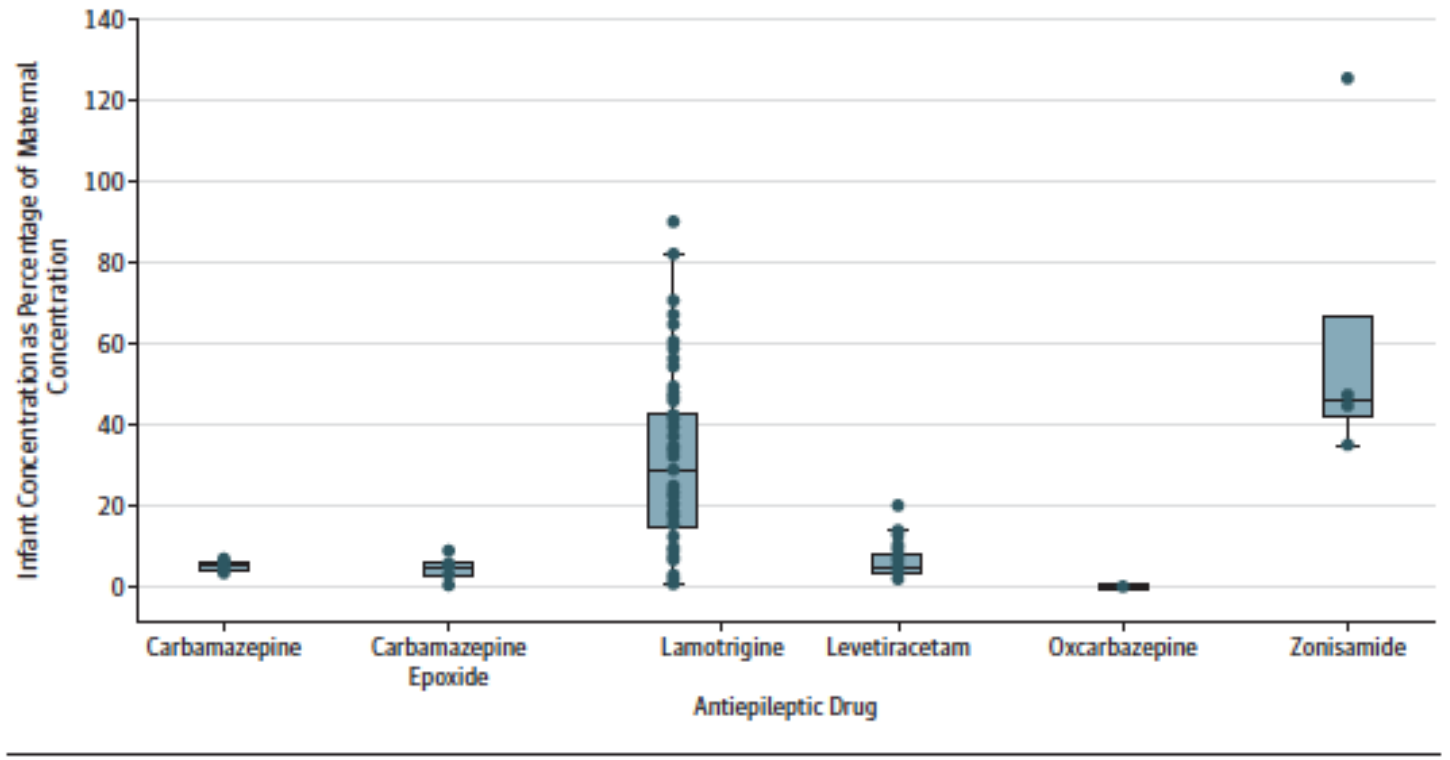
Mean placental passage of *ASMs*

(Umbilical Cord/Maternal blood venous samples)



Bank, Stowe, Newport, Pennell, *Epilepsia* 2017.

Percentage of infant to mother plasma concentrations



Box plots represent 25%ile and 75%ile.

40 /54 infants exposed to LEV were < LLoQ.

Birnbaum A, MONEAD, *JAMA Neuro*, Dec 30, 2019.

Neurodevelopmental effects of ASMs through breastmilk

- NEAD study and breastfeeding: Age 6 year-old cognitive outcomes
  - 44% of children were breastfed
  - Mean adjusted IQ scores:
    - 4 IQ points higher in the BF group
    - Higher verbal abilities

NEAD, neurodevelopmental effects of antiepileptic drugs
Meador, et al. *JAMA Pediatr.* 2014;168(8):729–736.

Suggestions for delivery/postpartum period

- Dose ASMs accurately
- Have the patient bring her medications to the hospital (same time/formulation)
- Epidural anesthesia recommended; allows periods of less than maximal intensity of physical stressors during labor and delivery
- Lorazepam/IV ASMs should be available during labor and delivery as needed for acute seizure control
- Risk for seizures may be increased peripartum (sleep deprivation)
- Postpartum ASM tapers are established based on individual factors
- Breastfeeding is supported, with possible neurodevelopmental benefits, but with implementation of strategies to lessen sleep deprivation
- Counseling about signs of depression and action plans if symptoms develop
- Safety precautions with the newborn (no co-sleeping, bathing the baby alone)
- Confirm postpartum contraception

ASM, antiseizure medication; IV, intravenous.
Voinescu PE and Pennell PB. *Semin Neurol* 2017;37:611–623.

THANK YOU!