Epilepsy Management in women – challenges

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AIIMS

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J. KIFFIN PENRY EPILEPSY MINIFELLOW NETWORK

UCLA

Overview

1. Puberty & Menstruation
2. Catamenial epilepsy
3. Gender specific side effects of AED
4. Cosmetic side effects of AED
5. **Fertility**
6. **Contraception**
7. **Pregnancy**
8. Sexual dysfunction
9. Menopause
10. Osteoporosis

- 95% pregnancies – good outcome

Magnitude of WWE

- **Seizures & related issues arise at any stage of a woman's life.**
- **Approx 1.3- 1.5 million WWE are of childbearing age**
- **& 3–5 births/1000 are of WWE**
- **Pregnant WWE constitute 0.5% of all pregnancies**
- **25-30% of WWE – increase in sz frequency during pregnancy**
- **95% pregnancies – good outcome**
- ***Goal- effective control of maternal seizures with least risk to fetus***

Pennell PB. Pregnancy, epilepsy, & women's issues. Continuum.2013

Epilepsy in women

- **Epilepsy is one of the common chronic disorders affecting women of reproductive age.**

Morrell M. Epilepsy in women. Am Fam Physician 2002; 66: 1489–94.

- **Maternal mortality 10-times higher in WWE than in those without.**

Table 1. The maternity, maternity mortality, and epilepsy-related mortality figures for the trienniums between and including 1991–2008 (adapted from CMACE[2])

Triennium period	No. of maternities	No. of maternal deaths	No. of deaths due to epilepsy	Proportion of epilepsy-related deaths	Rate of epilepsy-related deaths per 100,000 maternities
1991–1993	2,315,204	228	9	0.04	0.39
1994–1996	2,197,640	268	19	0.07	0.86
1997–1999	2,123,614	242	9	0.04	0.42
2000–2002	1,997,472	261	13	0.05	0.65
2003–2005	2,114,004	295	11	0.04	0.52
2006–2008	2,291,463	261	14	0.05	0.61

Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 2014; 55:e72–74

Original article

Epileptic Disord 2008; 10 (4): 282-9

Psychosocial impact of epilepsy in women of childbearing age in India

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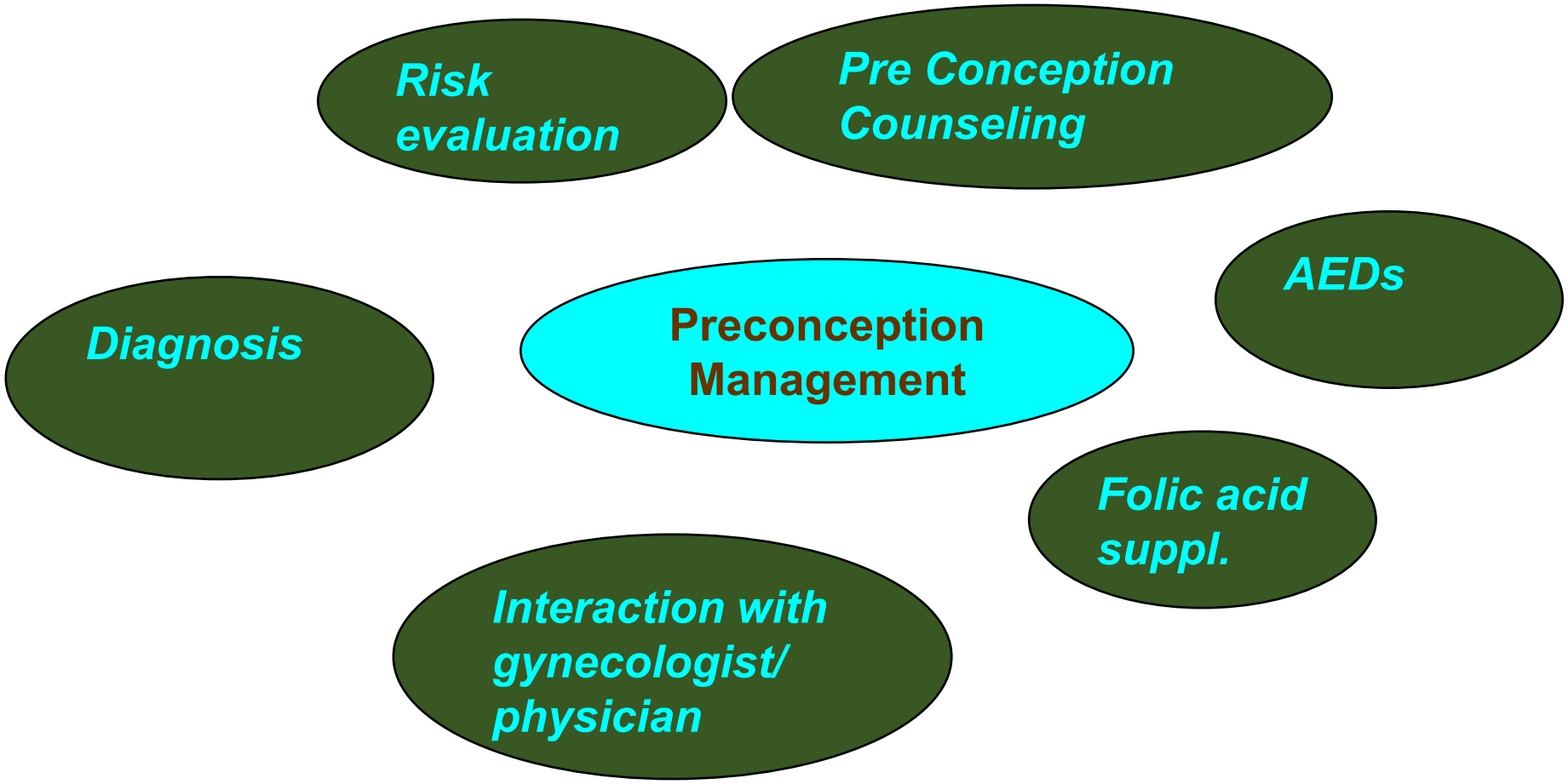
Preconception Management



Seizure frequency during pregnancy

Seizure frequency in pregnancy :

- Increase in 20-33%
- Decrease in 7-25%
- No change in 50-83%

Seizure frequency during delivery – 3.5%

The effect has many potential causes including

- hormonal effects,
- compliance
- metabolic changes
- falls in AED blood levels,
- change in sleep pattern
- tiredness
- psychological factors

1. Pennell PB. *Epilepsia* 2008;49(Suppl 9):43-55
2. EURAP Study Group. *Neurology* 2006;66(3):354-360

Changes in AED blood levels during pregnancy

levels of some AEDs fall significantly during pregnancy, especially in the third trimester, resulting in risk of increased seizures

- Decreased absorption
- Increased metabolism,
- Decreased protein binding
- Decreased GI motility in late pregnancy
- Fluid retention
- **Increased renal clearance**

LTG is particularly affected, levels fall on average by approximately 40-80%

Other drugs also sometimes significantly affected, include :

OXC, VPA, LEV, PHT, PHB, ZSM & CBZ

Frequent blood level monitoring is recommended

Preconception baseline level very impt

1. de Haan GJ, *et al. Neurology* 2004;63(3):571-3
2. Tomson T, *et al. Epilepsia* 2013;54(3):405-414

A first seizure during pregnancy

Trimester	Potential Causes
First	Metabolic alterations, medications, & toxicology screens
Second	Normal pregnancy-related physiological changes can result in lower blood pressure & dilatation of vascular spaces, & therefore syncopal events are a primary consideration
Third	In the third trimester, diagnoses such as eclampsia, PRES & CVT/CVA
Any trimester	Mass lesions, infections, & sudden events from vascular malformations

Sveberg L. Seizure 2015; 28: 35-8

Risks due to Seizures in Pregnancy

Non convulsive seizures	• Do not usually affect outcome of pregnancy
Convulsive seizures increased risk	• premature labour • fetal anomalies • fetal death • small for date babies
Status epilepticus	• Carries significant maternal & foetal risks

1. EURAP Study Group. *Neurology* 2006;66(3):354-360
2. Shorvon SD, Perucca E, Engel J (eds). 2009. Treatment of Epilepsy (3rd Edition) Wiley-Blackwell, Oxford.
3. Harden CL. *Continuum (Minneap Minn)* 2014:20(1):60-79

Risks due to Seizures in Pregnancy

Peripartum Seizure Risk

Highest risk in 3 peripartum days (Kerala Registry)

Seizures during delivery may have cardiac effect on foetus.

Focal > gen
3rd & 6th month
Greatest if 1 mo prior preg seizures
Epilepsia 2012

Thomas SV. Neurol India, 2001; 49 : 60-66

Management

Epilepsy per say is not an indication for CS.

Mother should carry their own AEDs to hospital

It should be taken as per routine schedule.

AED Teratogenicity

- Teratogenicity can be considered under three separate headings
  - Major malformations
  - Foetal antiepileptic drug syndromes
  - Long-term effects on learning & cognitive function
- Different drugs carry different risks
- Effects dose dependent & depend on the stage of pregnancy at which exposure occurred.
- Many of the major malformations detectable with high pick up rates with prenatal scanning
- Teratogenic risk of newer drugs is less known.
- Polytherapy increases the risk.
- Risks of malformation in a 2nd pregn higher if there was a malformation in first

1. Pennell PB. *Epilepsia* 2008;49 (Suppl 9):43-55. 2. Harden CL. *Continuum (Minneap Minn)* 2014:20(1):60-79
3. Tomson T & Battino D. Lancet Neurol 2012;11:803-13

Teratogenicity of VPA

VPA carries highest teratogenic risk: 6-9% of VPA exposed pregnancies result in malformations[1]

- risk is dose dependent (4% at doses below 700mg/day, >20% in 1500mg/day or more)
- malformation rate of VPA with LTG is 9%[2]
- Malformations include: spina bifida, congenital heart, hypospadias, skeletal defects
- VPA also causes a characteristic foetal syndrome with abnormal craniofacial development, minor skeletal abnormalities & developmental delay
- VPA exposure also carries a risk of long-term cognitive & learning disabilities:
- NEAD study: VPA exposed children at age of 6 yrs had sig lower IQ (mean 97. CI 94-101)

  CBZ exposed children (mean105, CI 102-108) &

  LTG exposed children (mean 108, CI 105-110) &

  PHT exposed children (mean 108, CI104-112)[3]
- Increased risk of autism & ASD[1]

1. Harden CL. *Continuum (Minneap Minn)* 2014:20(1):60-79
2. Tomson T & Battino D. Lancet Neurol 2012;11:803-13
3. Meador KJ, *et al*; NEAD Study Group. *Lancet Neurol* 2013;12(3):244-252

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

Incidence of Overall MCMs	
AEDs	Odds Ratio (OR)
Ethosuximide	3.04
Valproate	2.93
Topiramate	1.90
Phenobarbital	1.83
Phenytoin	1.67
Carbamazepine	1.37
Gabapentin	1.00
Lamotrigine	0.96
Levetiracetam	0.72

11 polytherapies; Significantly more harmful than control

Seizure 28 (2015) 46–50

Review

Major congenital malformations in children of women with epilepsy

Torbjörn Tomson[a,*], Hai Xue[b], Dina Battino[c]

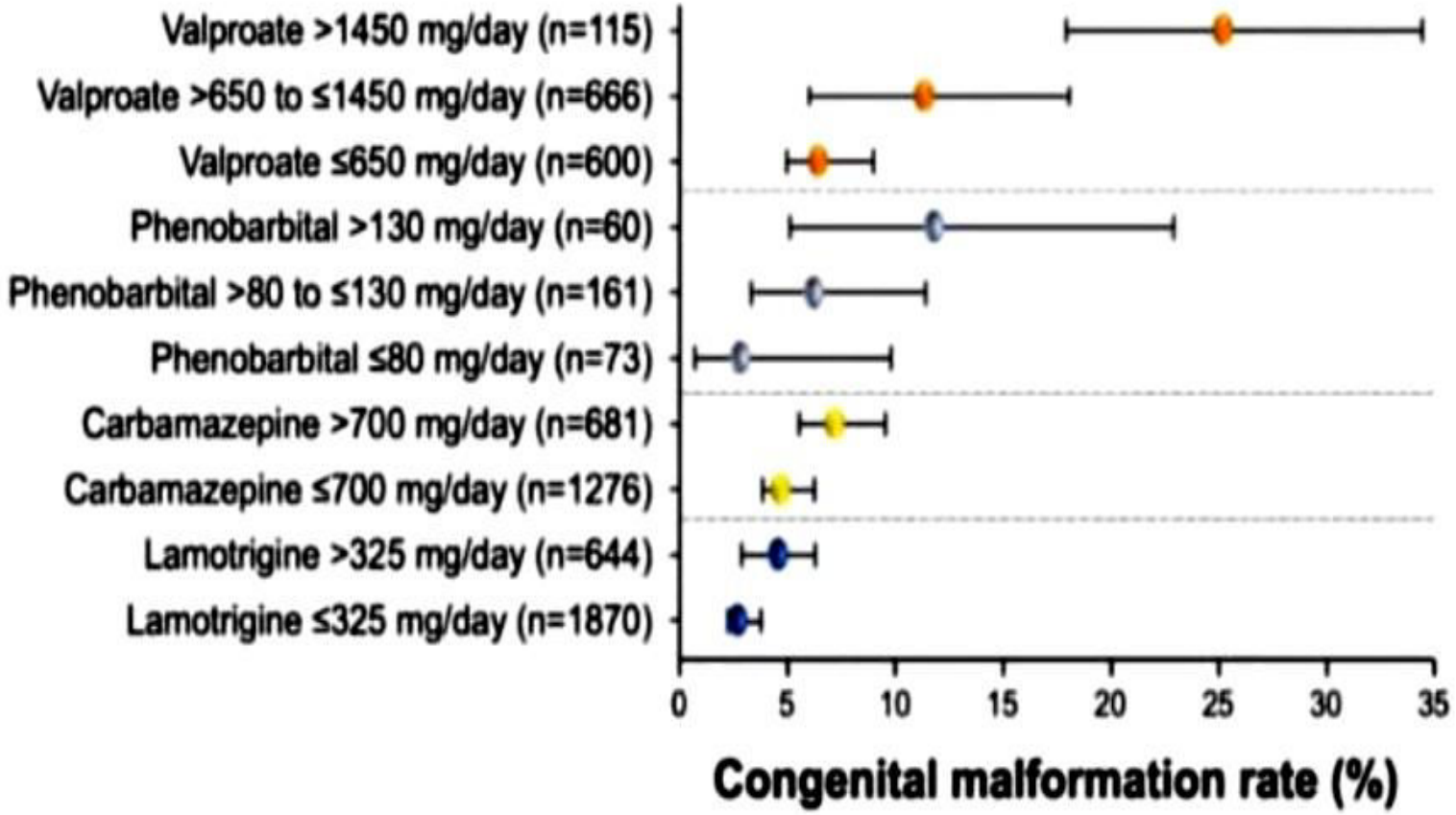
[a] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Department of Functional Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China
[c] Epilepsy Center, Department of Neurophysiology and Experimental Epileptology, I.R.C.C.S. Neurological Institute "Carlo Besta" Foundation, Milan, Italy

Overall MCMs prevalence with **8 common monotherapies**

Data from "Prospective Registers"

Source	VPA (%)	CBZ (%)	LTG (%)	PB (%)	PHT (%)	LEV (%)	OXC (%)	TPM (%)
EURAP Europe/Aus/ Kerala	9.7 (10.3)	5.6(5.5)	2.9 (2.9)	7.4 (6.5)	5.8 (6.4)	1.6 (2.8)	3.3 (3.0)	608 (3.9)
NAAPR Us/Canada	9.3	3.0	1.9	5.5	2.9	2.4	2.2	4.2
UK (Ireland)	6.7	2.6	2.3		3.7	0.7		4.3
AUS Australia	13.8	5.5	4.6		2.4	2.4	5.9	2.4
NMBR Scandinavia	6.3	2.9	3.4	7.4		1.7	1.8	4.2
SMBR Sweden	4.7	2.7	2.9		6.7	0		
GSK (int)			2.2					

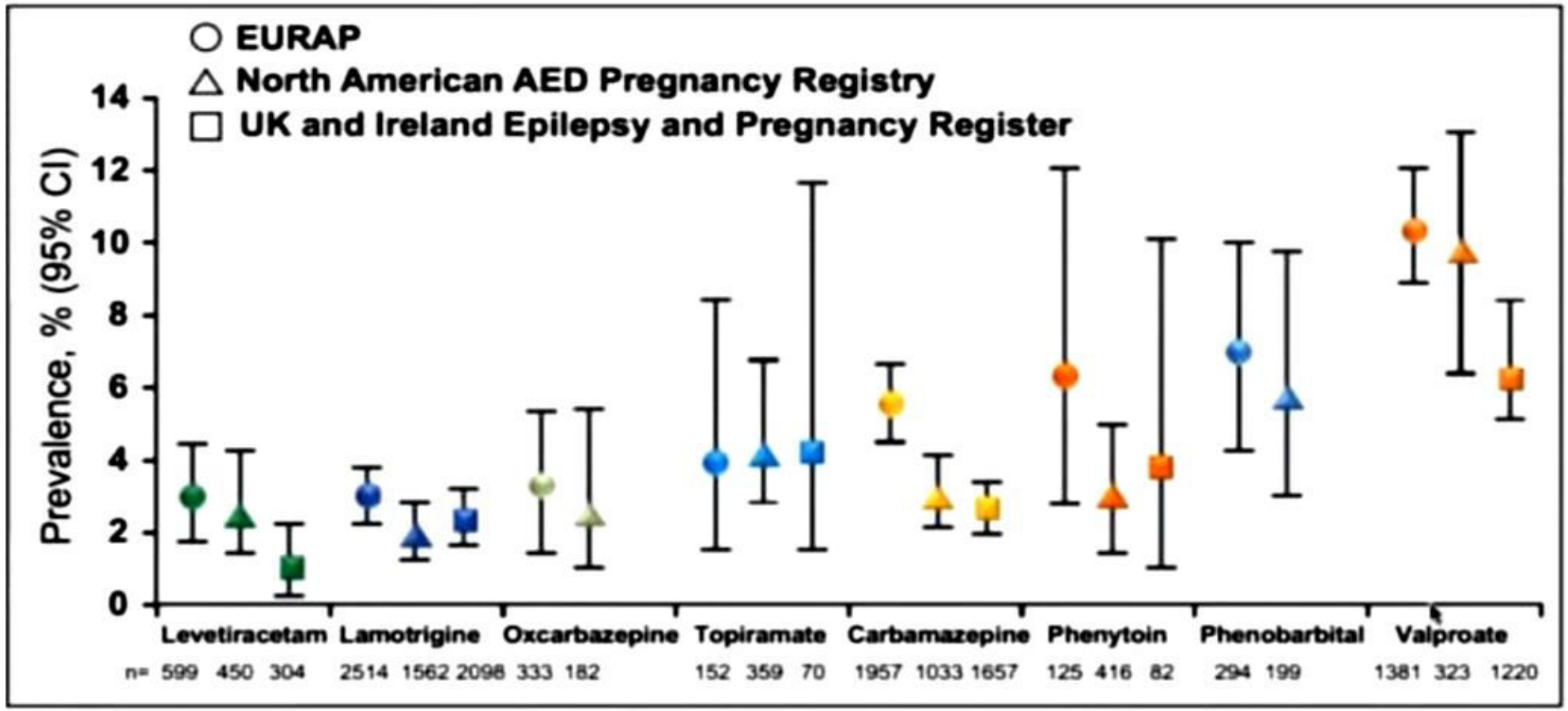
Dose-dependency of malformations after prenatal exposure to 4 ASM monotherapies : EURAP data



Courtesy of Emilio Perucca and Torbjörn Tomson

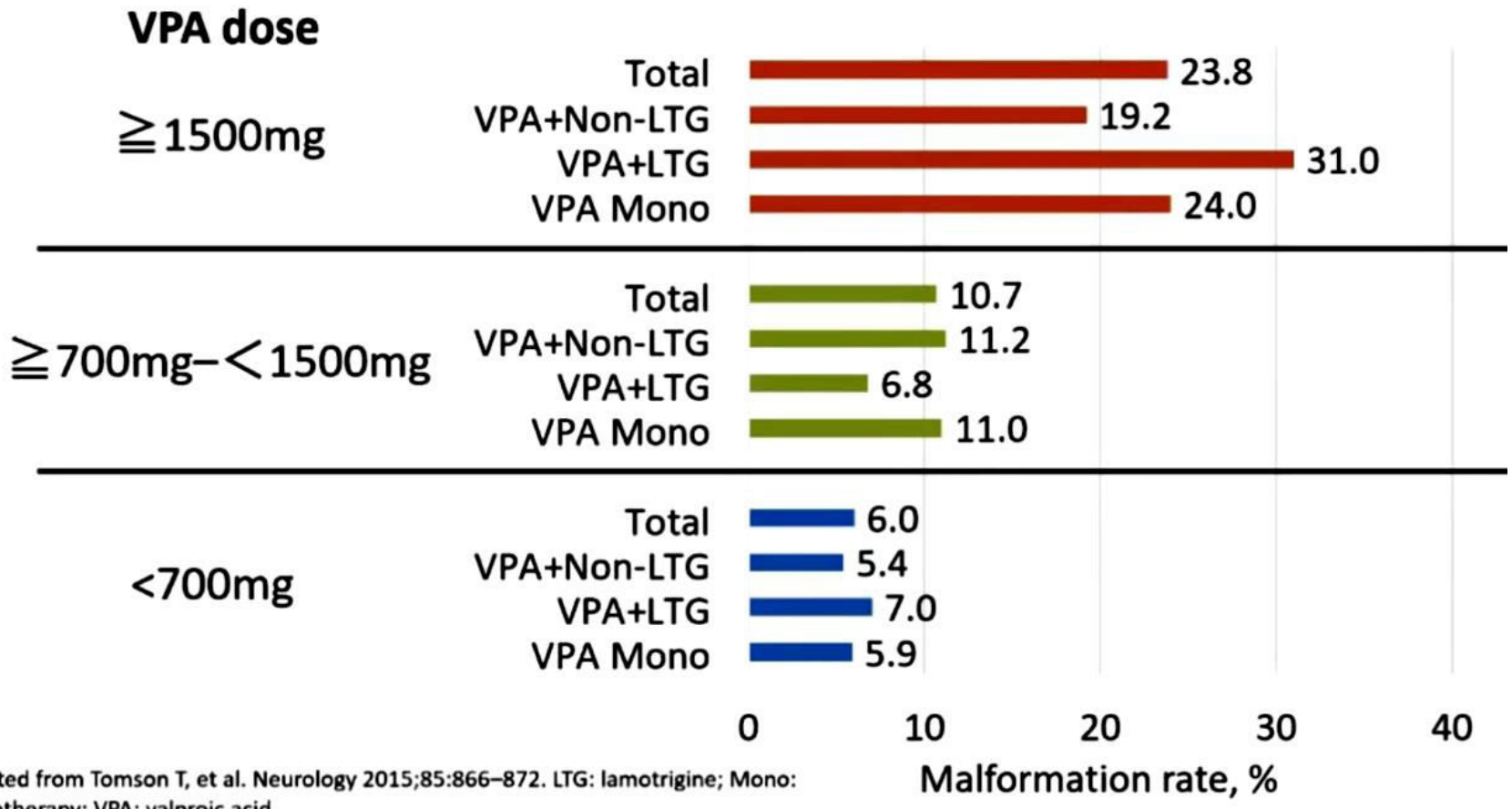
Adapted from Tomson T et al. *Lancet Neurol* 2018;17:530-8

Frequency of malformations after prenatal exposure to 8 ASM monotherapies : Data from 3 pregnancy registers



Adapted from Tomson T et al. *Curr Opin Neurol* 2019;32:246-52

Comparison of Malformation Rates among VPA Mono, VPA+LTG and VPA+ (Other Non-LTG)



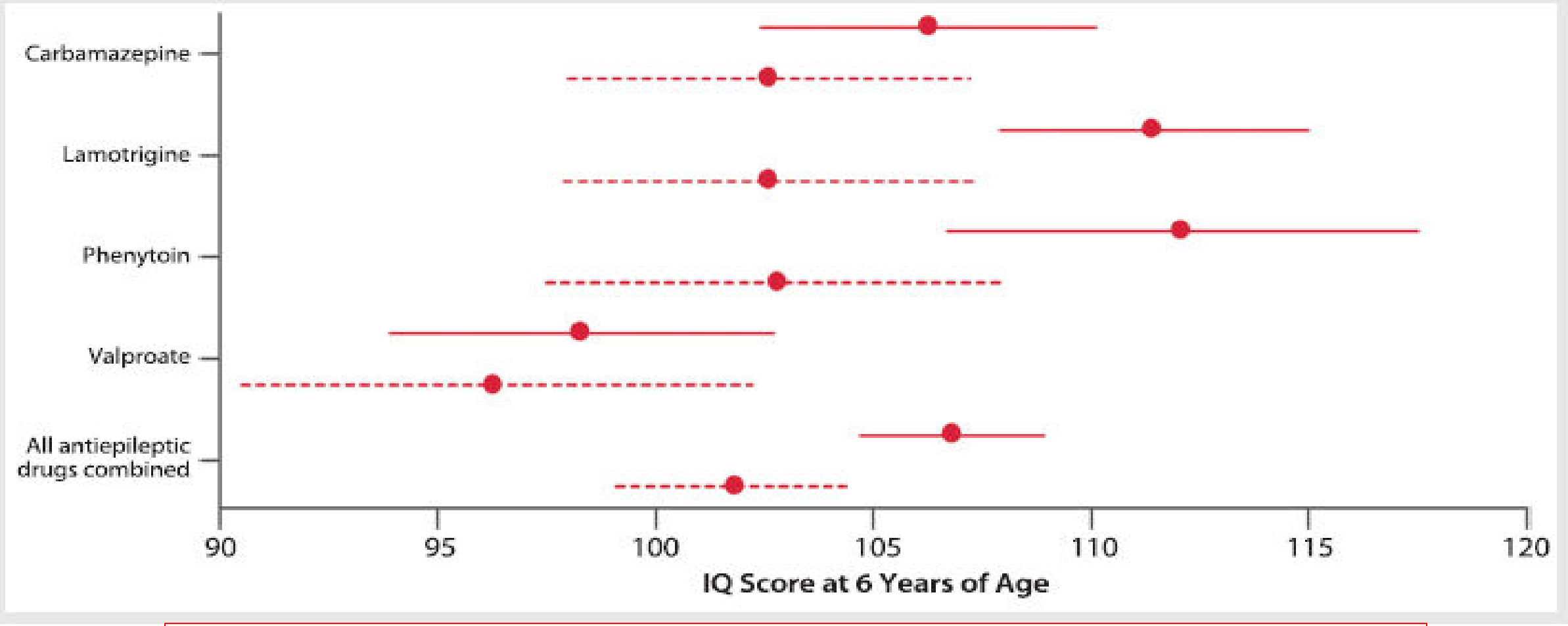
Adapted from Tomson T, et al. Neurology 2015;85:866–872. LTG: lamotrigine; Mono: monotherapy; VPA: valproic acid.

Teratogenicity of some of the newest ASMs

	Risk of major congenital malformations	Risk of adverse neurodevelopment outcomes	Other risks
Brivaracetam	**?**	**?**	**?**
Cenobamate	**?**	**?**	**?**
Eslicarbazepine acetate	**?**	**?**	**?**
Lacosamide	**?**	**?**	**?**
perampanel`	**?**	**?**	**?**

? = unknown / unclear risks

IQ at 6 yrs on AED with & without Folate



Meador KJ, et al; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013

……. Without folate, ▬▬ With folate

Advising women preconception in epilepsy

Pre-conception counseling – advice to women planning pregnancy

1
- **Best to consult prior to pregnancy so that a treatment strategy can be devised & drug changes can be made prior to pregnancy[1,2]**

2
- **Confirm diagnosis & assess need for treatment with AEDs**
- **Explain need to balance risk v benefit[1,2]**

3
- **Review genetic risk factors & counsel appropriately[2]**

0.4-0.8 mg of folic acid daily

1. Scottish Intercollegiate Guidelines Network (Guideline 70): http://sign.ac.uk/guidelines/fulltext/70/section4.html
2. Harden CL. *Continuum (Minneap Minn)* 2014:20(1):60-79

Folic acid supplementation

- Folate deficiency during pregnancy
- low birth weight
- premature delivery
- Miscarriage
- congenital malformations
- PIH
- FMs esp NTDs
- Recommended in all PW esp PWWE (x2>) to prevent FMs
- Prospective epilepsy pregnancy registries report
  - No association b/w periconceptional F/A intake & ↓ MCMs risk
  - Improved IQ scores in 6-year-old children of WWE_FA pre-conception
- Dose used b/w 0.4 mg/day as per each specific clinical case
- Lack clear guidelines
- EI & older ASMS high-dose recommended
- ? newer ASMS (LTG, LEV)

Research

JAMA Neurology | Original Investigation

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

JAMA Neurol. 2022;79(11):1130-1138. doi:10.1001/jamaneurol.2022.2977
Published online September 26, 2022.

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

cohort study, identified 3 505 882 singletons born in Denmark (1997-2017), Norway (2005-2017), & Sweden (2006-2017) from the national medical birth registers.

association between increased risk of cancer among children of mothers with epilepsy & maternal use of high-dose folic acid.

In contrast, prenatal exposure to high-dose folic acid not associated with an increased risk of childhood cancer in children born to mothers without epilepsy.

Management during pregnancy

Lifestyle & Nutrition

- Minimize chance of convulsive seizures by lifestyle advice
- Continue folate 0.5mg/day

Monitoring

- Alpha feto protein prenatal diagnosis & ultrasound scanning if appropriate 14-16 wk
- Monitor clinical status of epilepsy & where appropriate AED drug levels

Dose of AED

- Manage drug doses in last trimester by monitoring blood levels
- Readjust dose rapidly in the post-partum period

Walker SP, *et al. BJOG* 2009;116:758-767

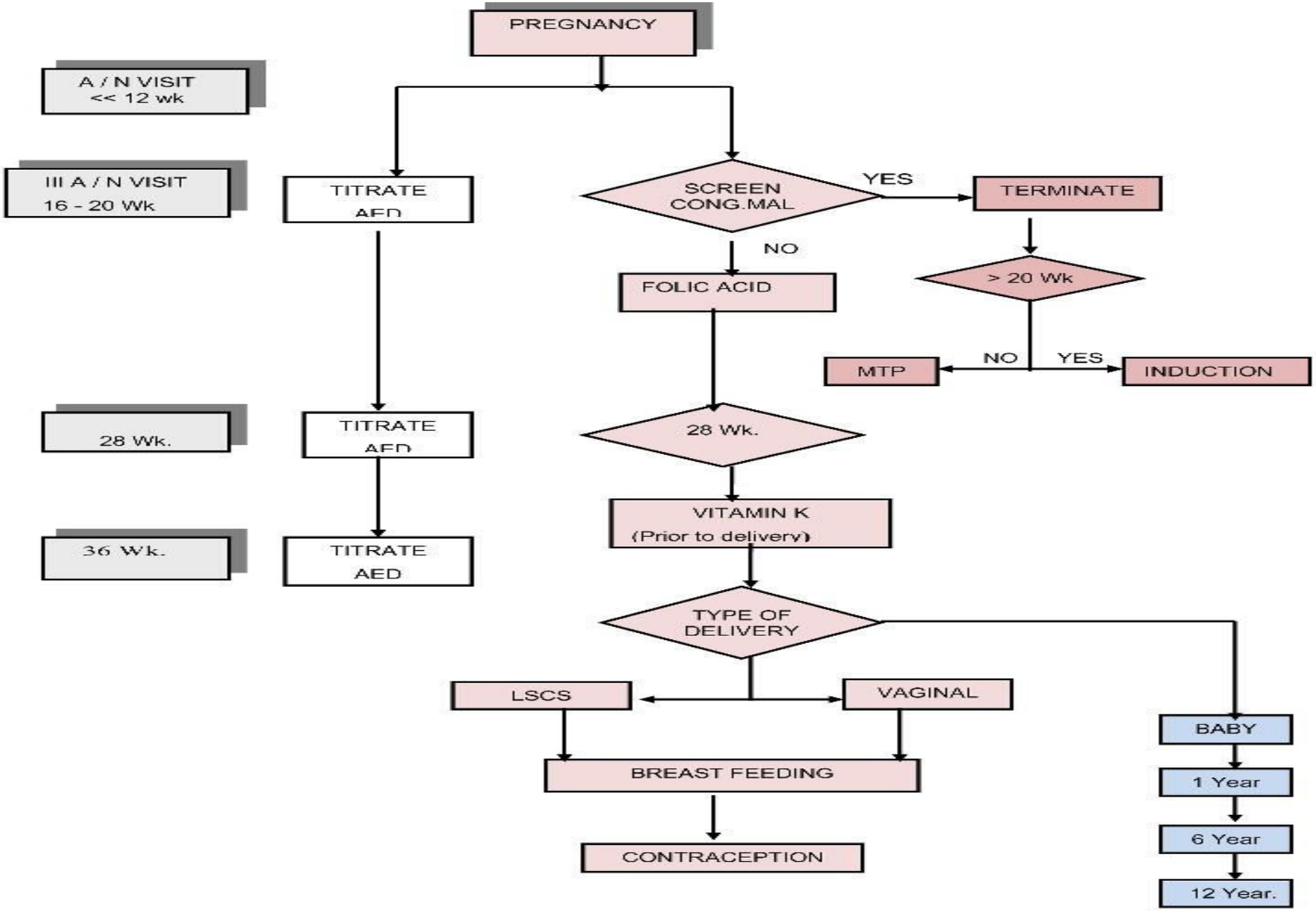
Advising women preconception in epilepsy

- **Modify treatment according to risk v benefit analysis:[1,2]**
  - **Aim for monotherapy where possible**
  - **Aim for lowest effective doses and blood levels**
  - **For some drugs split doses to avoid high peak levels**
  - **Consider option of no AED treatment (especially in first trimester)**

- **Avoid VPA in all, except those where risks of VPA are clearly less than its benefits[1,2]**
- **All attempts to make major changes should be made before pregnancy[2]**
- **Recommend folate 0.5 mg/day[1,2]**
- **High doses of folate has increased number of spontaneous abortions & in animal studies showed adverse effect on fetal brain development with reduced seizure threshold.** **(Al Asadi, Seizure:2015)**

1. Scottish Intercollegiate Guidelines Network (Guideline 70): http://sign.ac.uk/guidelines/fulltext/70/section4.html
2. Harden CL. *Continuum (Minneap Minn)* 2014:20(1):60-79

ALGORITHM FOR MANAGEMENT OF EPILEPSY AND PREGNANCY



Breast feeding & AED exposure

IQs of children of women taking AEDs who were breast fed were compared with those who were not breast fed:

Breastfed	**108 (105:111)**
Non-breastfed	**104 (101:106)**
Mean adjusted* IQ scores at age 6 yrs (95% CI) across all AEDs	**4 (0:8), p=.04**

(181 children, 43% breastfed, mean duration of 7.2 months)

➡

Encourage breastfeeding

*** Adjusted for other significant factors in the model (i.e., maternal IQ, AED group, AED dose, periconceptional folate, and breastfeeding) plus the propensity score.**

Meador et al. *JAMA Pediatr*. 2014 168(8):729-36

Breast feeding & AED exposure

Levels in breast milk % maternal blood concentration	AEDs
Low levels of the following drugs are found in breast milk (i.e. 20% or less of maternal blood concentrations) These are unlikely to cause any pharmacological effects	CBZ, GBP, LEV, OXC, TPM & VPA
Levels of the following drugs have potential pharmacological effects (i.e. <50-60% of maternal blood concentrations)	ESM, LTG
Levels of the following drugs can be clinically significant (ie > 50-60% of maternal blood concentrations):	PHB

Tomson T. In The Treatment of Epilepsy. Eds Shorvon S, Perucca E, Engel J. Wiley-Blacxkwell, Oxford 2009: p328

Puberty & epilepsy

Rise in levels of FSH & LH- Gradual increase in estrogen

Estrogen is **e**pileptogenic & **P**rogesterone is **p**rotective

Marked increase of estrogen prior to ovulation might be of importance for changes in seizure pattern

Epileptic activity affect endocrine function at hypothalamic level, including LH pulsatality

Roste LS, et al. Eur J Neurol. 2003;10(5):501–6

Catamenial epilepsy

Pathophysiological determinants[1]

- The neuroactive properties of reproductive steroids
- The variation of neuroactive steroid levels across the menstrual cycle
- the susceptibility of the epileptic substrate to neuroactive steroid effects

Commonly recognized patterns[1]

- **First pattern perimenstrual (C1: Day -3 to +3)**
- **Second pattern – peri-ovulatory (C2: Day 10 to -13)**
- **Third pattern – entire luteal phase in Anovulatory cycles (C3: Day 10 to -3)**

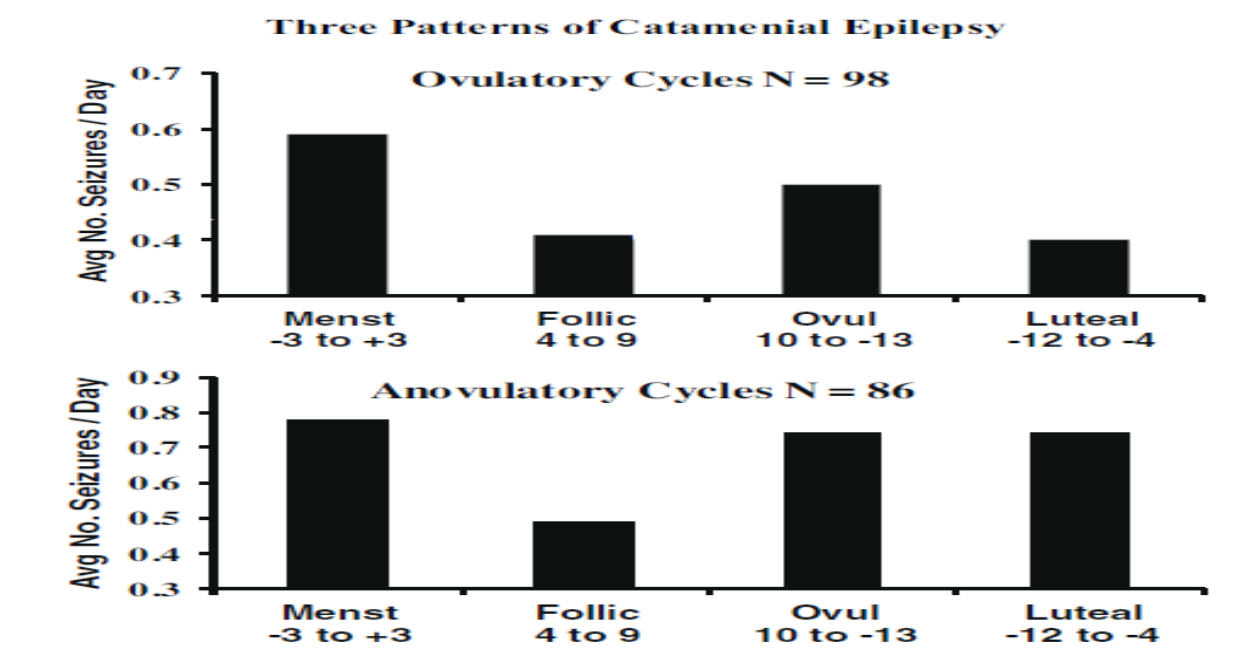


Fig.

Sound evidence for the existence of catamenial epilepsy[1]

1. Herzog AG. Seizure 2015; 28 :18–25

Catamenial epilepsy

Altering fluid electrolyte balance[1] → Use of acetazolamide or diuretics

Cyclical AED treatment[1] → Cyclical change in dose of current AED or Add another AED before menstruation

Hormonal intervention[1] → Premenstrual progesteron, antiestrogen (Clomiphene), GnRH agonist

Class 3 evidence for adjunctive progesterone treatment of the perimenstrually exacerbated subtype.[2]

Treatment regimen of Progesteron 200 mg[2]

Day 14 to 25	
A whole logenze	Three times in a day
Day 26 & 27	
½ logenze	Three times in a day
Day 28	
¼ logenze	Three times in a day

No logenzes until the next day 14

1. Roste LS, et al. Eur J Neurol. 2003;10(5):501–6
2. Herzog AG. Seizure 2015; 28 :18–25

Epileptic Disord 2016; xxx (x): 1-5

A case of recurrent status epilepticus and successful management with progesterone

Bhargavi Ramanujam, Amit Arora, Varun Malhotra, Deepa Dash, Santosh Mehta, Manjari Tripathi

All India Institute of Medical Sciences, New Delhi, India

Received July 20, 2015; Accepted November 24, 2015

ABSTRACT – Catamenial epilepsy (CE) is a commonly observed phenomenon among women with epilepsy, the management of which is both hormonal and non-hormonal. Progesterone therapy has been tried in these patients, as the possible mechanism of CE is withdrawal of progesterone and a higher oestrogen/progesterone ratio in the perimenstrual and periovulatory periods. Here, we describe a 24-year-old female with multiple seizure types since childhood, which became refractory to adequate antiepileptic drug therapy after menarche with catamenial clustering of seizures. She went on to have several episodes of non-convulsive status epilepticus also with similar periodicity, which would abate only with midazolam infusion,

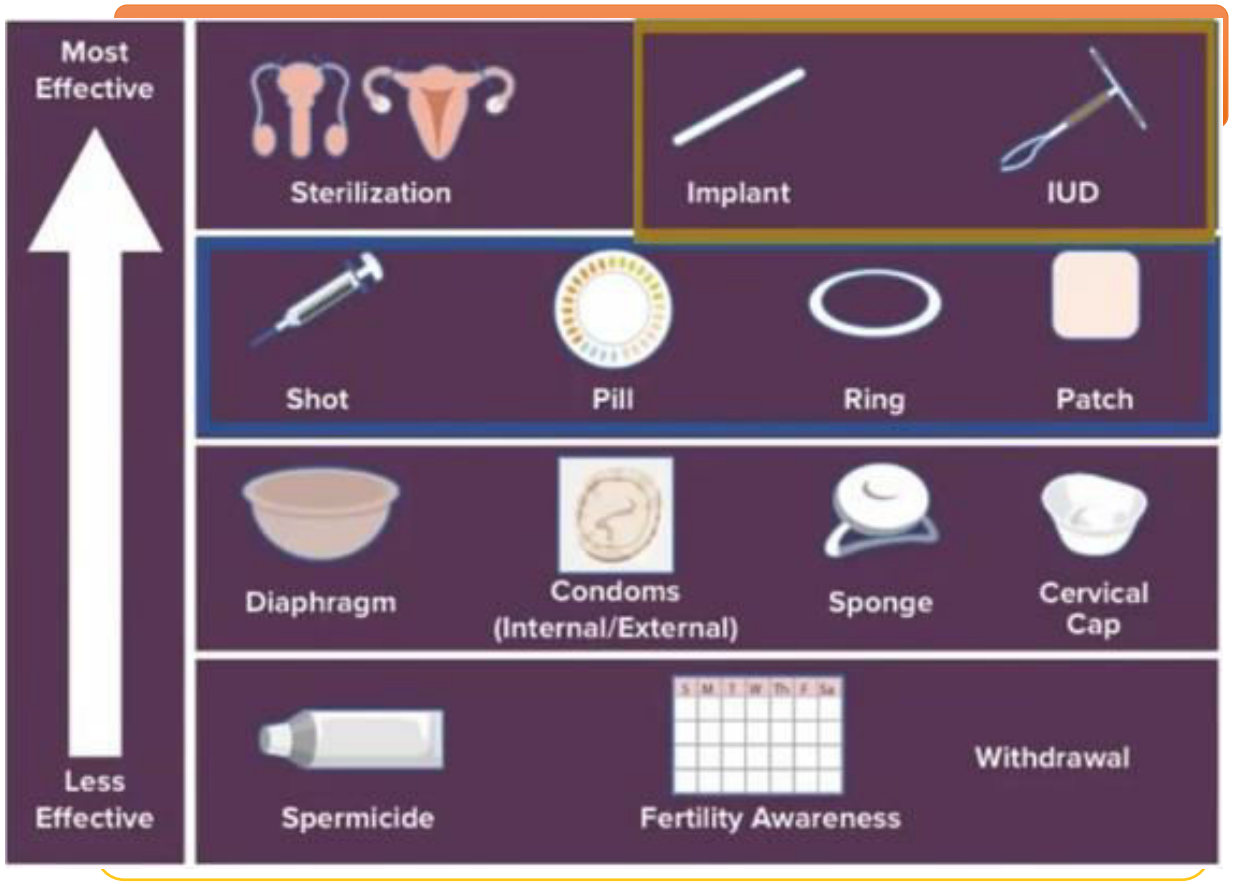
AED treatment & contraception

Some AEDs **reduce** levels of the hormones in the combined oral contraceptive pill (COC) & so risk contraceptive failure.

Effects are due to liver enzyme **induction, especially of the oestrogen** component

Differential effects on progesterone & oestrogen levels can be complex, & prediction of contraceptive **failure** can be difficult

COC also induce the metabolism of some AEDs, lowering their blood levels



1. O'Brien MD & Gilmour-White SK. Postgrad Med J 2005;81:278–285
2. Scottish Intercollegiate Guidelines Network (Guideline 70): http://sign.ac.uk/guidelines/fulltext/70/section4.html

Interaction of AEDs with COC

AEDs reduce levels of OC	OCs reduce levels of AEDs	No significant interactions
Phenobarbital[1,3]	Valproate[3,4]	Benzodiazepines[1]
Phenytoin[1,3]	Oxcarbazepine?[4]	Gabapentin[1,3]
Primidone[1,3]	Lamotrigine[3,4]	Lacosamide[2]
Carbamazepine[1,3]		Levetiracetam[1,3]
Oxcarbazepine[1,3]		Pregabalin[1,3]
Felbamate[3]		Tiagabine[1,3]
Eslicarbazepine[2]		Vigabatrin[1,3]
Topiramate (≥200mg)[1,3]		Zonisamide[1,3]
Rufinamide[3]		Retigabine[2]
Lamotrigine[3]		

1. O'Brien MD & Guillebaud J. *Epilepsia* 2006;47:141 9-22 ; 2. Chung SS. European Neurological Journal 2009;1:1-11
3 .Schwenkhagen AM & Stodieck SR. Seizure 2008;17:145-50 ; 4. Johannessen SI & Landmark CJ. Current Neuropharmacology 2010;8:254-67
5. European Medicines Agency. Accessed on 31 October 2012. Available from
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002434/WC500130815.pdf

Epilepsy & Menopause

- **Perimenopause**
  - **Fluctuations in ovarian steroid levels may exacerbate or diminish seizures[1,2]**

- **Menopause**
  - **Seizures may improve[2]**
  - **Improvement most likely in those with catamenial pattern[2]**
  - **HRT with menopause may worsen seizures[2]**

HRT= hormone replacement therapy

[1.] Abbasi F, et al. *Epilepsia.* 1999;40(2):205-210.
[2.] Harden CL, et al. *Epilepsia.* 1999;40(10):1402-1407.

AEDs & Osteoporosis

- AEDs may influence the risk of fracture in persons with epilepsy. AEDs most commonly associated with altered bone metabolism and decreased BMD are inducers of the cytochrome P450 enzyme system, including PHT, primidone, & PHB.
- PHT use has been associated with increased fracture risk.
- Although CBZ is also an enzyme-inducing AED, current data are less consistent.
- VPA, a cytochrome P450 enzyme inhibitor, is also associated with an increased risk of alterations in bone and mineral metabolism and decreased BMD.
- Polytherapy may independently result in increased abnormalities of bone metabolism.

Noe KH & Alison MP. Continuum Lifelong Learning Neurol 2010;16(3):159–178.

Bone health

- **Most recommended AEDs**

  LEV, LTG , TPM, VGB, Gabapentin

.

.

Alison M Pack. The Association Between Antiepileptic Drugs and Bone Disease .Epilepsy Curr. 2003 May; 3(3): 91–95

Together **E**veryone **A**chieves **M**ore

THANK YOU……

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