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Pregnancy and Cavernoma

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Little Evidence to Inform Practice

Issues:

Genetics and option of PGD

Risk of bleeding

Imaging / MRIs in pregnancy

Surgery

Seizures and anti epileptic drugs in pregnancy

Mode of delivery

Genetics and PGD

Familial form = Autosomal dominant = 50% risk

Must know the gene defect to have PGD

PGD unit must apply for permission if not treated someone with same mutation before to get license

IVF creates embryos from mother's egg and father's sperm

Embryos are tested for the gene

Those not carrying the mutation are frozen and then replaced (embryo transfer)

Same risks / success rates as IVF for other conditions / subfertility

Risk of bleeding in pregnancy

Traditionally thought to be increased

CCM more likely to grow because of higher levels of estrogen and progesterone

Increased vascular growth factors eg. VEGF

Yamada et al. Neurol Med Chir (Tokyo) 2013; 53: 555-60

Annual incidence of bleeding = 0.6-0.7%

Increased risk of bleeding:

Rebleeding – 4.5% / year

Familial CM – 1.1% / year (particularly CCM3)

CMs of brainstem – 2.5-5% / year

CM > 1cm

Age < 35 years

Associated venous anomalies

Witiw et al. Neurosurgery 2012

186 patients from University of Toronto Vascular Malformations Study Group

349 pregnancies (283 live births)

49 hemorrhages during childbearing years

3 during pregnancy

None during delivery or within 6 weeks post partum.

Hemorrhage rate pregnant = 1.15% (95% CI: 0.23-3.35) per person-year

Non pregnant = 1.01% (95% CI: 0.75-1.36) per person-year

Relative risk of pregnancy was 1.13 (95% CI: 0.34-3.75) (P = .84).

Neurosurgeons and obstetricians were the source of most hemorrhage risk advice. The majority of neurosurgeons suggested that the risk was unchanged, but the obstetricians were divided. Four patients never conceived, and 2 others began contraception because of the advice that they received.

Kalani MY, & Zabramski JM. J Neurosurg. 2013 Jan;118(1):50-5.

168 pregnancies among 64 female patients with CCM Barrow Neurological Institute CCM natural history study, Phoenix, Arizona, US

28 sporadic and 36 familial

Symptomatic hemorrhage (defined as new-onset or exacerbation of seizure activity or any change in neurological status) occurred during 5 pregnancies (most common symptom = seizures (4 cases))

Risk for symptomatic hemorrhage was 3% per pregnancy

1.8% per pregnancy in the sporadic group

3.6% per pregnancy in the familial patients.

19 deliveries by cesarean section: 5 for obstetrical reasons, 8 for fear of possible hemorrhage, and 6 for unknown reasons.

Vaginal delivery was performed without complications for the remaining 149 pregnancies.

Risk of Bleeding

Joseph NK, Kumar S, Brown RD, Lanzino G, Flemming KD. Influence of Pregnancy on Hemorrhage Risk in Women With Cerebral and Spinal Cavernous Malformations. Stroke. 2021 Jan;52(2):434-441. Mayo clinic, US

90 women (< 46 years old) CM brain or spinal cord

Mean age 31.6 years

25.6 % familial; 46.7% with haemorrhage; 24.4% brain stem

136 pregnancies before CM diagnosis; 36 pregnancies at / after diagnosis

4 women had haemorrhage during pregnancy / postpartum leading to diagnosis

402.6 years of f/u:

Non pregnant 42 bleeds = 10.4% per year (95% CI 7.5-14)

Pregnant [32 pregnancies = 26.9 years] 0 bleeds = 0% per year (95% CI 0-13.6%)

No difference between bleeding risk pregnant vs. non pregnant

No bleeds during delivery. Vaginal delivery safe

Risk of bleeding: Conclusions

The risk of intracranial hemorrhage from cerebral cavernous malformations is likely not changed during pregnancy, delivery, or post partum.

The authors' experience suggests that the risk of symptomatic hemorrhage from a CCM during pregnancy is not increased and that a history of CCM is not a contraindication to pregnancy or vaginal delivery.

Imaging

MRIs safe in pregnancy (spine and brain)[1]

Gadolinium contrast

- **essential for adequate preoperative evaluation**
- **associated venous anomalies**

large retrospective study[2] of first trimester exposure with gadolinium (n = 397)

- slight increase in stillbirths / neonatal death aRR 3.70 (95% CI 1.55–8.85) may be related to the condition necessitating the MRI rather than the GAD
- significant increase in a composite outcome of rheumatological/inflammatory/infiltrative skin conditions (aHR 1.36 95% CI 1.09–1.69)
- no increase in connective tissue or skin disease resembling nephrogenic systemic fibrosis, a syndrome associated with gadolinium exposure outside of pregnancy.

[1]Lowe S. Diagnostic imaging in pregnancy: Making informed decisions. Obstet Med. 2019;12(3):116-122.

[2]Ray JG, Vermeulen MJ, Bharatha A, et al. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 2016; 316: 952–961.

Radiology Guidelines

Guidelines for diagnostic imaging during pregnancy and lactation. ACOG 2017

- The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome.
- Breastfeeding should not be interrupted after gadolinium administration.

Surgery in pregnancy

General anaesthetic safe

Delay until after delivery if >32 weeks

Indications include:

- **symptomatic haemorrhage / progression**
- **rebleed**
- **family history**
- **venous anomaly**

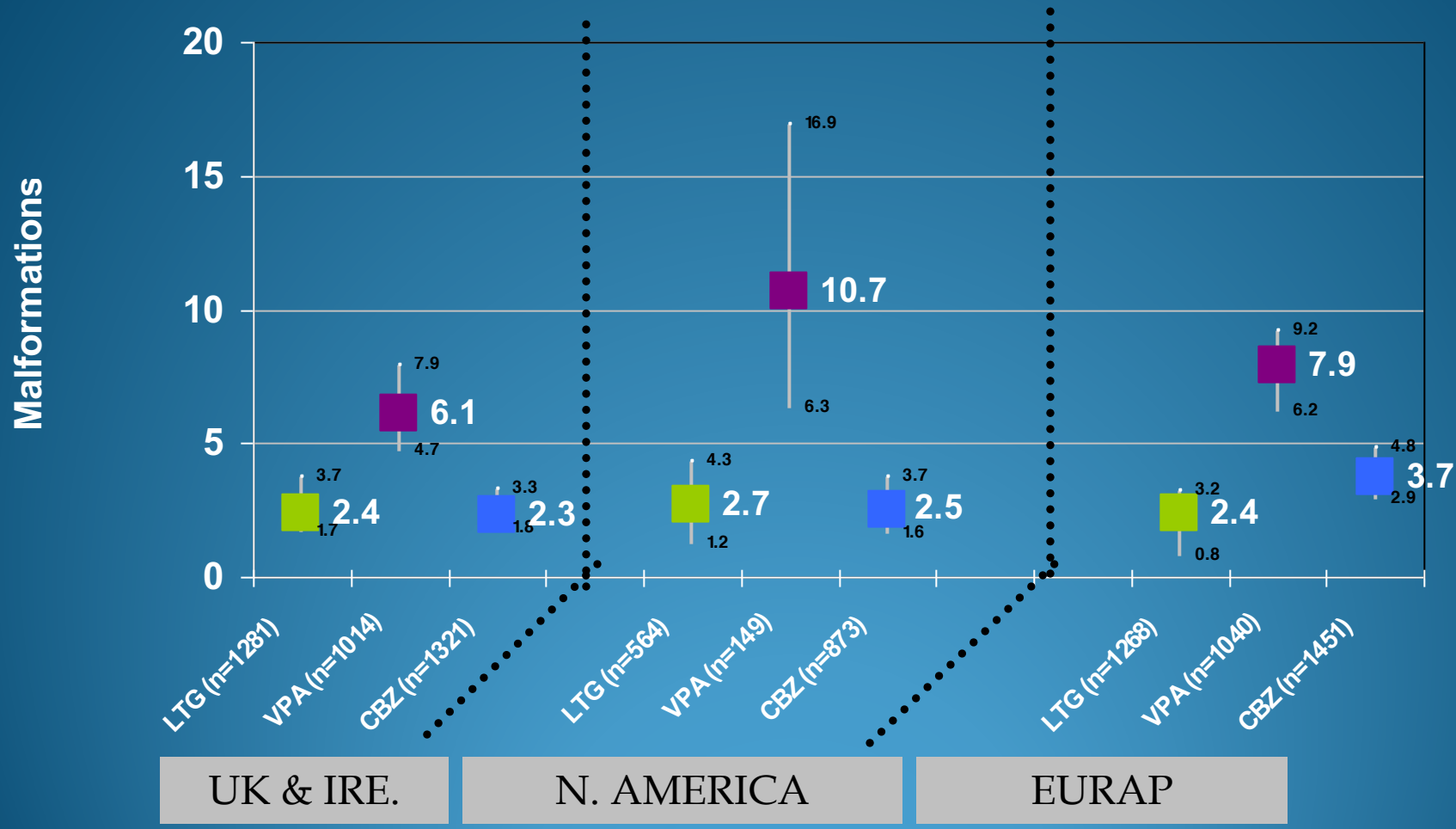
Seizures and AEDs in pregnancy

Single seizure unlikely to harm baby

Recurrent generalized seizures harmful to mother and baby

Risk of congenital malformations with AEDs

MCM rates following AED exposure during first trimester



Morrow et al. ECE 2010
Wyszynki et al. 2005 Neurology 64: 961-965; Holmes et al. 2004 Arch Neurol, 61: 673-678
Tomson et al ECE 2010

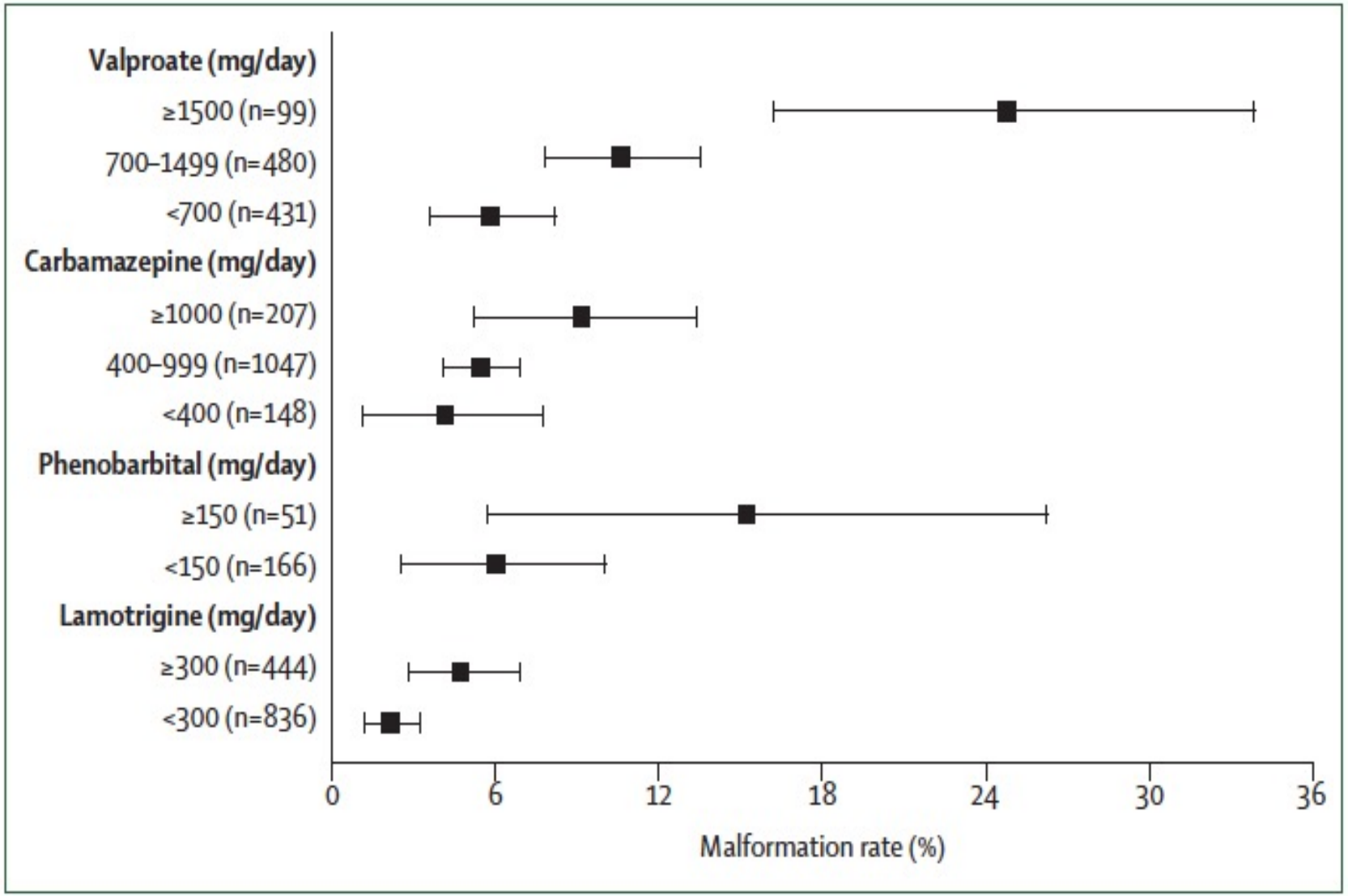
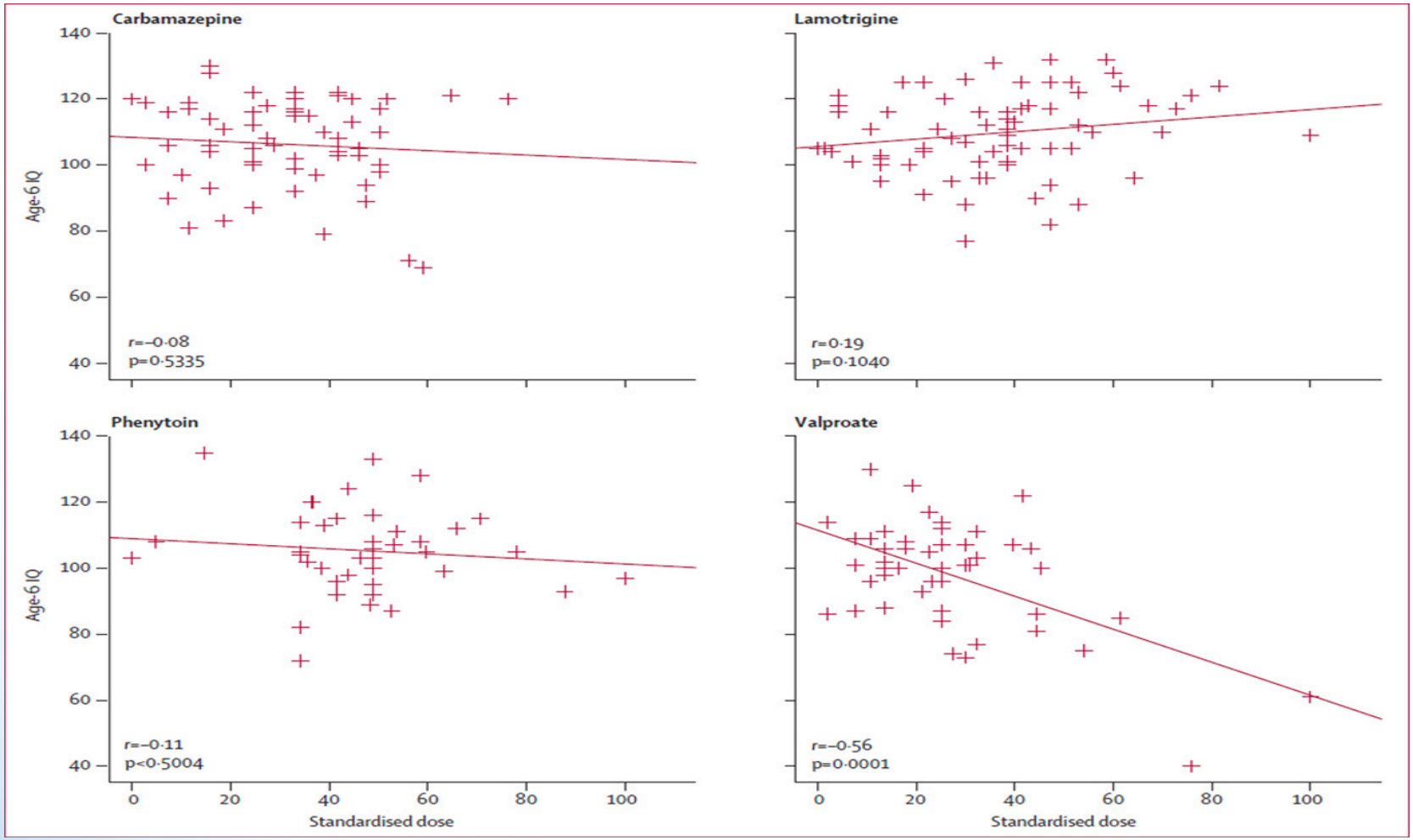


Figure 3: Rates of major congenital malformations at 1 year after birth in relation to exposure to antiepileptic drug monotherapy

Data from EURAP.[30] Bars are 95% CI.

Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study
Age-6 IQ and maternal IQ for every antiepileptic drug during pregnancy



Meador, et al. Lancet Neurol. 2013 March;12(3):244-252.

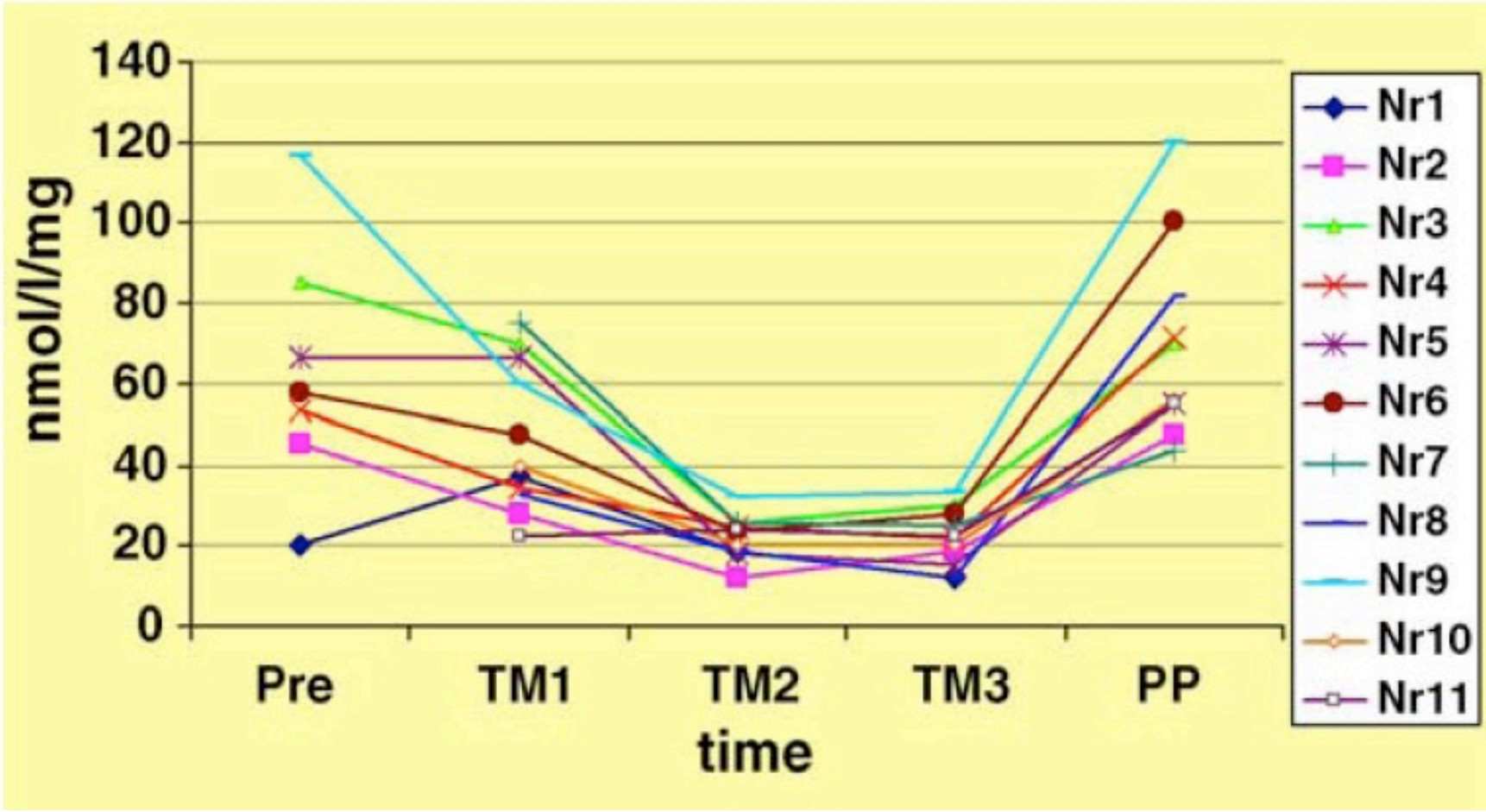
MHR Epilepsy medicines where data support increased risk of birth abnormality

Lamotrigine and levetiracetam medicines are safer to use during pregnancy than other epilepsy medicines. Information supports that they do not increase the risk of physical birth abnormalities compared with the general population

General population	2 to 3 out of 100 babies
Carbamazepine	4 to 5 out of 100 babies
Phenobarbital	6 to 7 out of 100 babies
Phenytoin	about 6 out of 100 babies
Topiramate	4 to 5 out of 100 babies
Valproate	about 10 out of 100 babies

https://www.gov.uk/government/publications/public-assesment-report-of-antiepileptic-drugs-review-of-safety-of-use-during-pregnancy/antiepileptic-drugs-review-of-safety-of-use-during-pregnancy. Jan 2021

Changes in plasma lamotrigine levels in pregnancy



LTG concentration / dose decreases by 65% in T2 and T3

Petrenaite V, Sabers A, Hansen-Schwartz J. Epilepsy Res. 2005 Jul;65(3):185-8.

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

- **Women with epilepsy taking antiepileptic drugs who become unexpectedly pregnant should be able to discuss therapy with an epilepsy specialist on an urgent basis. It is never recommended to stop or change antiepileptic drugs abruptly without an informed discussion.**
- **Pregnant women with epilepsy should have access to regular planned antenatal care with a designated epilepsy care team.**
- **RCOG Green-top guideline 68 (Royal College of Obstetricians and Gynaecologists 2016b)**

PRE-PREGNANCY COUNSELLING

Assess need for treatment

Optimize control

Monotherapy if possible (80% controlled with 1 or 2 drugs)

Counsel re teratogenesis

Give folate 5 mg / day

Valproate < 1g/day, divided doses, slow release formulation, consider stopping / changing

ANTENATAL CARE continued

- General advice to patient and her relatives
  - Avoid bathing
  - Teach recovery position
- Monitor drug levels baseline and then if seizures.
- Increase dose if seizures
- Increase lamotrigine anyway

INTRAPARTUM CARE

- Deliver in hospital
- Risk of seizures increased peripartum
- 1-2% intrapartum
- 1-2% within first 24 hours
- Do not stop AEDs in labour
- Use alternative route if high risk / previous seizure in labour
  - Clobazam orally
- Recurrent / prolonged seizures / status
  - IV lorazepam 4 mg; diazemuls 10 mg

POSTNATAL CARE

- Give neonate 1mg IM Vit K
- Do not leave unattended (beware the bath)
- Encourage breast feeding
  - Drug concentrations in milk are less than in blood
  - Blood levels in baby are < therapeutic
- Decrease dose after 2-4 weeks if increase was required in pregnancy

CONTRACEPTION

- Use combined OCP containing > 50 ug oestrogen or give 2 x 30 ug
  - Phenytoin, phenobarbitone and carbamezepine induce hepatic microsomal enzymes
- Use double POP / “morning after”
- Depoprovera standard dose OK
- Or use other form of contraception
- Valproate, lamotrigine, leveteracetam = non-enzyme inducing

Table 1 | Contraceptive options for women with chronic kidney disease

Contraceptive	Perfect-use failure rate (%)*	Typical-use failure rate (%)*
Safe and effective methods		
Progesterone-only pill	0.3	9
Progesterone intrauterine device	0.2	0.2
Progesterone-only subdermal implant	0.05	0.05
Female sterilization	0.5	0.5
Unsafe and/or ineffective methods		
Oestrogen-containing methods (pill, patch or ring)	0.3	9
Male condom	2	18
Female condom	5	21
No method	85	85

*% of couples experiencing an unplanned pregnancy in the first year of use. Data from REF. 36.

Mode of delivery

Should be determined by obstetric factors

No evidence that vaginal delivery increases risk of bleeding

Control pain / blood pressure with epidural (ensure antenatal meeting with obstetric anaesthetist – particularly if spinal cavernoma)

Thank you for your attention!