

# Sex Hormones, Sexuality and Fertility: Effects of Epilepsy and its Treatments

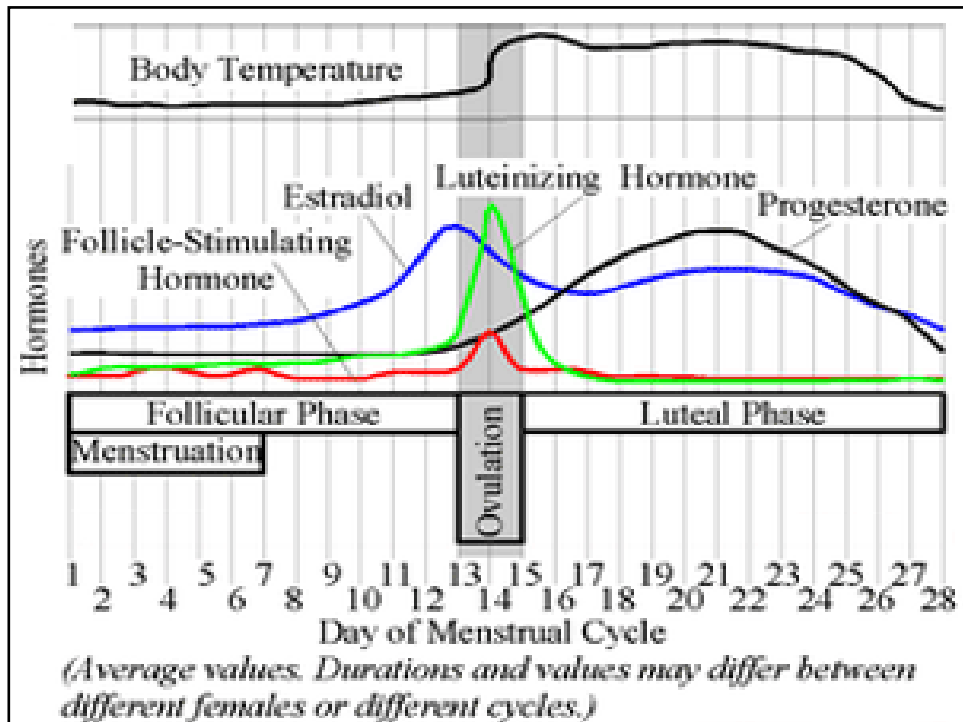
Associate Professor Beverley Vollenhoven  
Reproductive Endocrinologist and Infertility Specialist

Head of Gynaecology Southern Health, Department of Obstetrics &  
Gynaecology Monash University and Monash IVF, Melbourne

## Overview

Women with epilepsy may seek care by either a gynaecologist or a reproductive endocrinologist for:

- Contraception
  - Management of periods
- Management of catamenial epilepsy
  - Pre-pregnancy counseling
- Reproductive consequences of obesity  $\pm$  PCOS



## Reproductive Hormones

- E may ↓ seizure threshold by glutamate release, reducing inhibition at GABA receptor and increasing the number of excitatory neuronal synapses
- P may ↑ seizure threshold ? through allopregnanolone which activates GABA receptor

## Contraception

- Hormonal contraception is the most popular contraceptive choice in Australia
- 30% of women use either the COCP, Implanon or Depo-Provera

National Health Survey, Australia 2001

## The Contraceptive Challenge

- The majority of AEDs are liver enzyme inducers so increase both breakdown and protein binding of COCP and Implanon. If used 6% failure/year for COCP
- It is crucial to know the type of AED and its liver effect in order to prescribe hormonal contraception

Mattson et al JAMA 256, 238

# The Contraceptive Challenge

Rational polytherapy of focal epilepsies

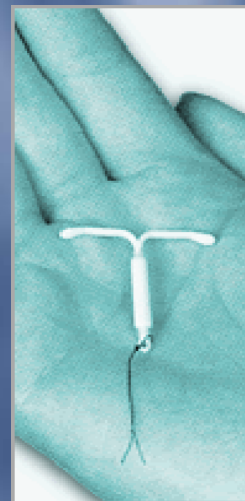
Table 4 Metabolic pathway, effect of AEDs on hepatic enzymes and drug-drug interactions (DDI)

AED	Metabolic pathway	Hepatic enzyme-inducers and hepatic enzyme-inhibitors <sup>25,26</sup>	DDI
Carbamazepine*	Hepatic	Enzyme-inducer (CYP2C,CYP3A,CYP1A2, microsomal epoxide hydrolases, UGTs) ****	Yes
Clobazam	Hepatic	No	No
Clonazepam	Hepatic	No	No
Ethosuximide	Hepatic	No	Yes
Gabapentin	Renal	No	No
Lamotrigine**	Hepatic	Enzyme-inducer (UGTs)	Yes
Levetiracetam	Renal	No	No
Oxcarbazepine*	Hepatic	Enzyme-inducer (CYP3A4 , UGTs) and enzyme-inhibitor CYP2C19)	Yes
Phenobarbitone*	Hepatic	Enzyme-inducer (CYP2C,CYP3A, microsomal epoxide hydrolases, UGTs)	Yes
Phenytoin*	Hepatic (90%)	Enzyme-inducer (CYP2C,CYP3A, microsomal epoxide hydrolases, UGTs)	Yes
Tiagabine***	Hepatic	No	Yes
Topiramate*	Hepatic <Renal	Enzyme-inducer (CYP3A4, b-oxidation ) and enzyme-inhibitor (CYP2C19)	Yes
Valproate	Hepatic	Enzyme-inhibitor (CYP2C9, microsomal epoxide hydrolases, UGTs)	Yes
Vigabatrin	Renal	No	No
Zonisamide	Hepatic	No	Yes

## Contraception

The choices are:

- Depo-Provera every 10 weeks (may raise seizure threshold)
- IUDs (hormonal and copper)
- Barrier methods
- High dose COCP (not available)



## Management of Periods

Adolescents often have heavy and painful periods. Treatment includes:

- COCP depending on AED. Sometimes effective contraception is more important and periods managed by NSAIDs

## Management of Periods

Older women can have heavy bleeding and pain due to pelvic pathology. If no pelvic pathology use

- Mirena IUD (hormone coated) with excellent effect and also contraceptive. The AED will not affect the efficacy of the Mirena

## Management of Catamenial Epilepsy

- 70% of women may have a relationship between periods and epilepsy
- Up to 40% have catamenial epilepsy
- Seizure patterns may change at puberty and after menopause

Herzog et al Epilepsia 38, 1082; Herzog et al Ann Neurol 56, 431

## Management of Catamenial Epilepsy

Three patterns:

- Pattern 1 - just before or during menstruation
- Pattern 2 - with ovulation
- Pattern 3 – with ↑E/P as occurs in anovulatory cycles???

Similar occurrence may be seen with COCP during pill free interval

Herzog et al Epilepsia 38, 1082; Herzog et al Ann Neurol 56, 431

## Management of Catamenial Epilepsy

No approved hormonal treatments

- Suppressive
- Cyclic

Herzog et al Epilepsia 38, 1082; Herzog et al Ann Neurol 56, 431

## Management of Catamenial Epilepsy

Management:

- COCP continuously (depending on AED)
- Depo-Provera
- P in luteal phase??
- Two former suppressive with steady state levels of E/P
- Latter cyclic. 2 open label trials have shown significant improvement using natural oral P. Current RCT

Herzog et al Epilepsia 38, 1082; Herzog et al Ann Neurol 56, 431

## Pre-Pregnancy Counselling

- Fertility rates may be reduced voluntarily or involuntarily
- AEDs associated with congenital abnormalities at a 2-3 times increased rate
- Valproate 1-2% incidence of NTD and carbamazepine 0.5-1%
- Other defects include orofacial defects, VSD and ↑ in minor malformations involving face and digits
- Behavioural and cognitive defects

Morrell Am Fam Phys 66, 1489; Perucca & Tomson Lancet 367, 1467; Morrell Epilepsy Currents 2, 31; Meador et al Neurol 67, 407

## Pre-Pregnancy Counselling

Serious adverse events including FDIU

- Valproate 20.3%. Dose dependent >900mg/day
- Phenytoin 10.7%
- Carbamazepine 8.2%
- Lamotrigine 1%

Meador et al Neurol 67, 407; Wyszynski et al Neurol 64, 961; Vajda et al Acta Neurol Scand 112, 137

## Pre-Pregnancy Counselling

- Other studies show 10.7% and 17.1% for valproate monotherapy and similar results over 14 other cohorts
- Lamotrigine may not be as safe as indicated
- ? First choice in women who want pregnancy ? carbamazepine

Meador et al *Neurol* 67, 407; Wyszynski et al *Neurol* 64, 961; Vajda et al *Acta Neurol Scand* 112, 137; Davenport *BMJ*, 333, 615

## Pre-Pregnancy Counselling

- Polytherapy worse than monotherapy especially if valproate is one of the drugs
- Use the most pregnancy friendly AED
- Don't stop medication when pregnant without discussion

Morrell *Epilepsy Currents* 2, 31

## Pre-Pregnancy Counselling

- If AED induces liver enzymes low serum folate and should be using 5mg folic acid supplement
- Valproate may interfere with folic acid metabolism and require similar dose

Morrell Epilepsy Currents 2, 31

## Pre-Pregnancy Counselling

- Seizure pattern may change due to non compliance or pharmacokinetics
- Mother gets 10mg oral Vitamin K in final month to prevent neonatal haemorrhage

Morrell Am Fam Phys 66, 1489

## Reproductive Consequences of Obesity ± PCOS

- PCOS is a heterogeneous condition
- 5-10% of the population
- PCO vs PCOS
- 2 different criteria for diagnosis:
  - NIH
  - Rotterdam

## Reproductive Consequences of Obesity ± PCOS

- Women with PCOS are generally overweight, have irregular periods and signs of hyperandrogenism
- Long term consequences include infertility, type II diabetes, heart disease and cancer of the endometrium
- Some women develop the condition with weight gain and the condition regresses with weight loss
- Drugs that cause weight gain may cause PCOS

## Reproductive Consequences of Obesity ± PCOS

- 20-40% of women with epilepsy have PCO, 13-25% have PCOS. No consistency in method of diagnosis
- Valproate increases ovarian T and adrenal DHEAS
- Women on Valproate gain weight

Isojarvi et al NEJM 329, 1383; Isojarvi et al Epilep 42, 305; Herzog et al Epilep 42, 305; Mikkonen et al Neurol 62, 445

## Reproductive Consequences of Obesity ± PCOS

- No conclusive evidence that women using valproate are at greater risk of PCOS if they **do not** gain weight
- The mainstay of treatment is weight and waist loss and other features of the condition are treated on their merits