

Epilepsy and pregnancy management

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Epilepsy

- > Epilepsy is a common neurological condition characterised by seizures (Tatum et al. 2004)
- > Epileptic seizures are caused by paroxysmal discharges of excessive and / or hyper-synchronous abnormal activity of cerebral cortical neurones
- > Drug use to control epilepsy in the population ranges from 4 to 9 per 1,000 (Wallace et al. 1998)
- > Most women with epilepsy will need to continue taking antiepileptic drugs in pregnancy to prevent the harmful effects of seizures
- > The treatment goal in pregnancy is to maintain a balance between an effective but low dose of a single antiepileptic drug and the harmful effects of seizures (Kaaja et al. 2002)

Literature review

- > In Australia, approximately 1,500 to 2,000 women on antiepileptic drugs become pregnant per year
- > Retrospective studies report a 2- to 3-fold increase in adverse pregnancy outcomes for women on antiepileptic drugs. These include:
 - > Miscarriage
 - > Major congenital malformations (neural tube defects, orofacial defects, congenital heart abnormalities and hypospadias)
 - > Minor congenital anomalies (hypertelorism, epicanthic folds and digital hypoplasia)
 - > Microcephaly
 - > Intrauterine growth restriction (Vajda et al 2002)
- > Pregnant women with untreated epilepsy are not at increased risk of having a baby with a birth defect (Holmes et al. 2001; Motherisk 2002)

Pre-pregnancy care

- > In order to enable informed decisions and choice, and to reduce misunderstandings, women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about
 - > Contraception
 - > Conception
 - > Pregnancy
 - > Caring for their baby and breastfeeding

Contraception

- > Advise all women with epilepsy of childbearing age that the risk of failure of oral contraceptive agents is increased several-fold if they are taking an enzyme-inducing antiepileptic drug (e.g. phenobarbital, phenytoin, carbamazepine, or primidone)

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Conception

- > Pre-pregnancy counselling should provide a clear understanding of the risks of uncontrolled seizures and the possible teratogenicity of anticonvulsant agents
- > Administer folic acid 5 mg / day (10 times the prophylactic dose) for 1 month before conception and continue during the first trimester to reduce the risk of folic acid deficiency-induced malformations in women on anticonvulsant drug treatment (Nulman et al. 1999)
- > Genetic counselling is required if both parents have epilepsy or the disease is inherited
- > Aim for seizure control at least 6 months before conception and, if possible, cease or use the lowest effective dose of a single anticonvulsant according to the type of epilepsy
- > If anticonvulsant drugs are required aim to achieve levels in the therapeutic range before conception

Pregnancy

- > Arrange review by a neurologist or specialist physician
- > Obtain complete blood picture and serum folate levels
- > Explain the importance of continuing anticonvulsant medication when this is necessary because of the maternal and fetal risks associated with convulsions
- > Women should be re-assured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury

Antiepileptic drugs (AEDs)

- > In Australia, the following commonly used antiepileptic drugs have been available for 20 years:
 - > Phenytoin (ADEC Cat D)
 - > Carbamazepine (ADEC Cat D)
 - > Sodium valproate (ADEC Cat D)
 - > Phenobarbitone (ADEC Cat D)
 - > Ethosuximide (ADEC Cat D)
 - > Primidone (ADEC Cat D)
 - > Clonazepam (ADEC Cat C)
 - > Sulthiame (ADEC Cat D)
- > In recent years new antiepileptic drugs have been released
 - > Lamotrigine (ADEC Cat D)
 - > Topiramate (ADEC Cat B3)
 - > Gabapentin (ADEC Cat B1)
 - > Oxcarbazepine (ADEC Cat D)
 - > Pregabalin (ADEC Cat B3)
 - > Tiagabine (ADEC Cat B3)

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- > Vigabatrin (ADEC Cat D)
- > Levetiracetam (ADEC Cat B3)
- > The following drugs are enzyme-inducing antiepileptic drugs
 - > Carbamazepine
 - > Phenytoin
 - > Phenobarbitone
 - > Primidone
 - > Oxcarbazepine
 - > Topiramate

Phenytoin

- > Narrow therapeutic window
- > Increased clearance rate during pregnancy (leading to decreased serum concentrations)
- > A fall in total serum phenytoin concentrations may lead to poor seizure control
- > Associated major malformations are facial clefts, congenital heart defects and urogenital defects
- > Other reported defects are dysmorphic facial and other features e.g. distal phalangeal hypoplasia (Morrow and Craig 2003)

Carbamazepine

- > Relatively slow absorption
- > Large peak-trough fluctuations can be minimised by using a controlled-release formulation (Nulman et al. 1999), but this may require higher doses
- > Associated with major malformations including neural tube defects in up to 1 % of exposed pregnancies, heart defects, inguinal hernia, hypospadias and hip dislocations
- > There have also been reports of reduced head circumference, weight and length at birth (Morrow and Craig 2003)

Sodium valproate

- > Rapidly absorbed
- > Therapeutic range – measuring levels is of limited value apart from checking compliance
- > Divided doses are preferred to avoid high peaks in serum concentrations
- > Exposure to valproate during early pregnancy is associated with a 1 to 2 % incidence of neural tube defects, especially with doses > 1,000 mg / day
- > Other defects include cardiovascular complications, urogenital malformations, skeletal defects; and facial dysmorphic patterns

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Phenobarbital and Primidone

- > Barbiturates are now less frequently prescribed due to their tendency to produce sedation and impaired cognitive function
- > Associated with congenital heart defects and facial clefts
- > Infants born after exposure to phenobarbitone or primidone in utero should be monitored for withdrawal symptoms for up to 6 weeks after birth

Ethosuximide

- > Clinical studies on congenital anomalies after exposure to ethosuximide in pregnancy are inconsistent
- > Animal studies report increased frequencies of skeletal, central nervous system and other anomalies

Clonazepam

- > Thus far there is little information on the frequency of congenital anomalies after treatment with clonazepam in pregnancy

New antiepileptic drugs

- > Gabapentin, lamotrigine, levetiracetam and vigabatrin have no antifolate effects (Nulmann et al. 1999)
- > Thus far there is no evidence of an increased incidence of human birth defects with the most of the new antiepileptic drugs (Vajda et al. 2003)
- > Lamotrigine has been associated with an increased rate of oral clefts, and the ADEC Category was changed in 1996 from B3 to Cat D
- > Lamotrigine levels decrease during pregnancy, due to increased clearance by the mother

Management

Antenatal

- > Physician / neurology review in each trimester
- > Document history of seizure activity
- > Maternal serum screening for alpha-fetoprotein at 14 – 20⁺6 weeks
- > Offer first trimester combined screening for aneuploidy with detailed early morphology
 - > Ensure the request form for obstetric ultrasound includes details of all antiepileptic drugs the woman is taking
- > Detailed ultrasound assessment of the fetus at 18 – 20 weeks gestation (looking particularly for heart, renal and neural tube defects)
 - > Ensure the request form for obstetric ultrasound includes details of all antiepileptic drugs the woman is taking
- > Monitor plasma anticonvulsant levels (not useful for valproate) every 1 to 2 months. If there is deterioration in seizure control, adjust dose accordingly
- > Women should be advised about the importance of proper sleep and medication compliance, particularly in the last trimester, when AED levels tend to be lowest
- > Women should be encouraged to participate in the Australian Pregnancy Register for Women on Antiepileptic Drugs: tel: 1800 069 722 (Vajda et al. 2003)



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Vitamin K₁

- > Enzyme inducing antiepileptic drugs:
 - > Carbamazepine
 - > Oxcarbazepine
 - > Phenobarbitone
 - > Phenytoin
 - > Primidone
 - > Topiramate
- > are known to cross the placenta and promote oxidative degradation of vitamin K₁ in the fetus
- > Consider antenatal prophylaxis with oral vitamin K₁ 20 mg per day in the last 4 weeks of pregnancy if enzyme-inducing drugs are used (Konakion® MM ampoules 10 mg / 1 mL have Therapeutic Goods Administration [TGA] approval for oral use)
- > If vitamin K₁ has not been given antenatally, administer intravenous vitamin K₁ 10 mg by slow injection over 5 minutes in labour or threatened preterm labour

Intrapartum

- > Most women with epilepsy will have a normal uncomplicated vaginal birth
- > Two to four percent of women with epilepsy will have a tonic-clonic seizure during labour or in the first 24 hours after labour
- > Tonic clonic seizures may result in fetal hypoxia
- > Birth should be arranged in a hospital with facilities for emergency caesarean section and maternal and neonatal resuscitation
- > Continue oral anticonvulsants
- > Ensure intravenous access
- > Paediatrician / neonatologist at birth

NOTE: Phenytoin and phenobarbitone are the only parenteral antiepileptics.

- > Women will not usually need parenteral anticonvulsants in labour unless they are vomiting and unable to take their usual anti-convulsant medication
- > Women who have missed their anticonvulsant doses for more than 12 hours may need a parenteral dose. Consult a physician or neurologist.
- > For women already on oral phenytoin, continue the same dose intravenously (divided doses)
- > If the woman is on a different anticonvulsant, she will require a **phenytoin loading dose (15 – 20 mg / kg)** followed by maintenance doses of 8 mg / kg / day, approximately 300 mg, twice daily intravenously or orally
- > Intravenous diazepam 5-10 mg can be used for acute seizure management in women on other anti-epileptic drugs

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Immediately following birth

- > Advise the mother that intramuscular vitamin K1 should be administered to the newborn immediately after birth, and is the preferred method
 - > 1.0 mg for term babies
 - > 0.5 mg for babies < 1.5 kg bodyweight
- > If vitamin K1 is preferred by the mother to be given orally, administer 3 doses of 2.0 mg
 - > Give first dose immediately following birth
 - > Second dose on day three to five
 - > Last dose at four weeks
- > Observe baby closely for signs of respiratory depression
- > Examine baby for signs of anticonvulsant and epilepsy-associated dysmorphism

Postpartum

Antiepileptic drugs

- > Continue antiepileptic drugs
- > Antiepileptic serum levels quickly revert to pre-pregnancy levels. Lamotrigine levels may increase and the dose will most likely need to be reduced

Newborn care

- > Some antiepileptic drugs (e.g. phenobarbitone and primidone) can result in drug accumulation in the newborn
- > Observe baby for level of alertness and signs of excessive drowsiness (may need to review breastfeeding)
- > Valproate may be associated with jitteriness
- > If maternal seizure control is poor there may be a risk of injury to the infant

Breastfeeding

- > As antiepileptic drugs are excreted in breast milk only in low concentrations encourage breastfeeding
- > **Lamotrigine requires caution** – If a rash occurs in the baby, breastfeeding should be ceased and the cause of the rash urgently established. (CYWHS Medicines and Drug Information Centre – 08 8161 7222 Mon- Fri)

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Contraception

- > The oral progestogen-only pill or progesterone implant (Implanon®) is unreliable contraception for women on the enzyme-inducing anticonvulsants
 - > Carbamazepine
 - > Oxcarbazepine
 - > Phenobarbitone
 - > Phenytoin
 - > Primidone
 - > Topirimate
- > but acceptable for women on the others with the exception of lamotrigine
- > Lamotrigine: Combined oral contraceptives may increase lamotrigine's metabolism, decreasing its concentration and efficacy (during the week when inactive combined oral contraceptive sugar pill is taken lamotrigine's concentration may rise); consider using an alternative contraceptive; contact one of the pregnancy drug information centres (AMH)
- > Medroxyprogesterone acetate depot injection can be used and most guidance suggests shortening the usual 12 weeks interval to 10 weeks for women taking enzyme-inducing AEDs
- > Levonorgestrel IUD (Mirena) is also a useful contraceptive in these circumstances
- > Sequential pills or combined pills containing less than 50 micrograms of oestrogen may be associated with an increased incidence of breakthrough bleeding, or contraceptive failure, and should be avoided
- > Women taking enzyme-inducing AEDs and the combined oral contraceptive should be advised:
 - > To take at least 50 micrograms of ethinyloestradiol (e.g. Microgynon 50) and to report any breakthrough bleeding. If breakthrough bleeding occurs the dose of ethinyloestradiol can be increased to 80 – 100 micrograms

Discharge counselling

- > Offer advice to women at risk of further seizure activity to minimise any injury risk to baby:
 - > Feed baby seated low or on floor
 - > Bath baby with another person present whenever possible
 - > Minimise carrying of baby
 - > Use a pram with an automatic brake

Follow up

- > Arrange neurological or general practitioner follow up before discharge

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Useful web site

The Australian Pregnancy Register of Antiepileptic Drugs for Women in Pregnancy with Epilepsy and Allied Conditions

http://www.epilepsy-society.org.au/pages/documents/APR_info.pdf

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Abbreviations

e.g.	For example
et al.	And others
AEDs	Anti epileptic drugs
mg	Milligram(s)
ADEC	Australian Drug Evaluation Committee
Cat	Category
CYWHs	Children Youth and Women's Health Service
TGA	Therapeutic Goods Administration
kg	Kilogram(s)
AMH	Australian Medicines Handbook
IUD	Intrauterine device

Version control and change history

PDS reference: OCE use only

Version	Date from	Date to	Amendment
1.0	22 June 04	06 July 09	Original version
2.0	06 July 09	23 Nov 10	Review
3.0	23 Nov 10	29 Nov 10	Review
4.0	29 Nov 10	current	

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Table 1

Classification of epileptic seizures according to clinical type

Partial (focal, local) seizures	
Simple partial seizures (consciousness not impaired)	With motor signs
	With somato-sensory or special sensory symptoms (simple hallucinations e.g. tingling, light flashes, buzzing)
	With autonomic symptoms or signs (e.g. epigastric sensation, pallor, sweating, flushing, pilo-erection and papillary dilatation)
	With psychic symptoms (disturbance of higher cerebral function) e.g. déjà vu, distortion of time sense, fear (usually involves impairment of consciousness)
Complex partial seizures (with impairment of consciousness)	With simple partial onset followed by impairment of consciousness
	With impairment of consciousness at onset
Partial seizures evolving to secondary generalized seizures (may be generalized tonic-clonic, tonic or clonic)	Simple partial seizures evolving to generalized seizures
	Complex partial seizures evolving to generalized seizures
	Simple partial seizures evolving to complex partial seizures and then evolving to generalized seizures
Generalised seizures (convulsive or non convulsive)	
Absence seizures	Impairment of consciousness alone or with: mild clonic, atonic or tonic components, automatisms and/or auto-nomic symptoms or signs
Myoclonic seizures	Short muscle contractions, usually lasting < 400 ms
Clonic seizures	A series of myoclonic contractions that regularly recur at a rate of 0.2 – 5/s
Tonic-clonic seizures	Tonic-clonic seizures involve a tonic phase, in which the muscles suddenly contract, causing the person to fall and lie rigid. Up to a minute later, the seizure enters the clonic phase, when the muscles begin to alternate between relaxation and rigidity. The person may lose bowel or bladder control. The seizure usually lasts for 2–3 minutes, after which the person remains unconscious for a while. On waking, the person is likely to have a headache and to be confused and tired
Atonic seizures	Cause a loss of postural tone. The result is loss of posture (head drops, falls) and are often preceded by a short myoclonic seizure
Unclassified seizures	

Adapted from: Luders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R *et al.* Semiological seizure classification. *Epilepsia* 1998; **39**:1006-13.



ISBN number:
Endorsed by:
Contact:

UNKNOWN
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Lamotrigine and Breastfeeding

SUMMARY

Lamotrigine is a newer anticonvulsant indicated for treatment of simple and complex partial seizures.

In mothers being treated with lamotrigine, breast milk levels of lamotrigine are relatively high. Infant plasma levels are about 30% with levels up to 50% being reported. However, adverse effects have not been reported in infants.

Lamotrigine clearance increases throughout pregnancy, and maternal dose increases are often necessary to maintain therapeutic effect. It is important to reduce the dose of lamotrigine after delivery as clearance reduces to pre-pregnancy levels within 2 to 3 weeks postpartum. In one report, a mother's lamotrigine dose was reduced more gradually than originally planned and the infant developed severe apnoea, requiring resuscitation.

Lamotrigine can cause rare, but potentially fatal skin reactions. Breastfed infants should be carefully monitored for side effects such as rash, including measurement of serum levels to rule out toxicity if there is a concern. If a rash occurs, breastfeeding should be ceased and the cause of the rash urgently established.

LAMOTRIGINE (LAMICTAL^R)

Physical Characteristics:

- Protein Binding ~55%
- Bioavailability ~ 98%
- Half-life (adults) ~24 hours
- Half-life (children > 6 yrs) ~8 hours
- Half-life (neonates) ~24 hours (*may be longer*)
- Milk-plasma ratio ~0.60

LACTMED^{R 1}

Breastfed infants whose mothers are taking lamotrigine have relatively high plasma lamotrigine plasma levels, averaging 30 to 35% of maternal serum levels; infant plasma levels up to 50% of maternal levels have been reported. Neonates are particularly at risk for high plasma levels because their ability to metabolise the drug by glucuronidation is limited.

Maternal plasma and milk levels can rise dramatically in the immediate postpartum period if the dosage is not reduced to the prepregnancy dosage.

Lamotrigine can cause rare, but potentially fatal skin reactions (eg. Stevens-Johnson syndrome and toxic epidermal necrolysis), which are more common in children.

If lamotrigine is required by the mother, it is not necessarily a reason to discontinue breastfeeding, because many infants have been breastfed without adverse reactions. However, breastfed infants should be carefully monitored for side effects such as rash, drowsiness or poor sucking, including measurement of serum levels to rule out toxicity if there is a concern.

If an infant rash occurs, breastfeeding should be discontinued until the cause can be established.

REPROTOX^{R 2}

In studies involving 18 infants whose mothers were taking lamotrigine^{3, 4, 5, 6}, nursed infants maintained plasma concentrations of approximately 30% of the mother's plasma levels. The dose to the infant was estimated to equal or exceed 0.2 to 1mg/kg/day 2 to 3 weeks postpartum (paediatric dose 0.5 – 5mg/kg/day), which in combination with slow elimination in the infants resulted in lamotrigine plasma concentrations comparable to those reported during active lamotrigine therapy. No adverse effects were seen in any of the infants.

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MEDICATIONS AND MOTHER'S MILK, Hale, T.⁷

Several studies have been reported on breast feeding women taking lamotrigine, the estimated dose to the infant in one study was approximated to 2-5 mg per day on a daily maternal dose of 200-300 mg. In another study the estimated dose to the infant of a mother receiving 200 mg/day lamotrigine was 0.5 mg/kg/day. A study of 6 breast feeding women taking 175-800 mg (mean = 400) mg/day resulted in average infant doses of 0.45 mg/kg/day. In another study authors suggested significant genetic variability in the infant's ability to metabolise lamotrigine and that close monitoring of infants plasma levels was recommended. In all studies no adverse effects in the infant was noted.

UKMiCentral (UK Drugs in Lactation Advisory Service)⁸

No reports of adverse effects. Significant amounts in milk. Monitor infant for adverse effects, especially rash. Blood level monitoring in infant may be necessary.

LAMOTRIGINE IN BREAST MILK AND NURSING INFANTS: DETERMINATION OF EXPOSURE⁹

Thirty women and their nursing infants participated in the study, providing a total of 210 breast milk samples. Infant plasma concentrations were 18.3% of maternal plasma concentrations. The theoretical infant lamotrigine dose was 0.51 mg/kg per day, and the weight-adjusted relative infant lamotrigine dose was 9.2%. No other adverse events were observed or reported in the breastfed infants.

SEVERE APNEA IN AN INFANT EXPOSED TO LAMOTRIGINE IN BREAST MILK¹⁰

A 16-day-old infant developed several mild episodes of apnoea that culminated in a severe cyanotic episode requiring resuscitation. The mother had used lamotrigine in increasing doses throughout pregnancy, and at the time of the apnoeic episodes, she used 850 mg/day. The mother developed a seizure after delivery, and a more gradual dose reduction than originally planned was advised by a neurologist. The infant was fully breast-fed, and the neonatal lamotrigine serum concentration was 4.87 µg/mL at the time of admission. The mother's lamotrigine serum concentration 17 days after delivery was 14.93 µg/mL. Breast-feeding was terminated, and the infant fully recovered. To the authors' knowledge, this is the first published report of a serious adverse reaction in an infant exposed to lamotrigine through breast milk.

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Revised October 2009 MT

ISBN number:
Endorsed by:
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