Clinical Guideline
Epilepsy and pregnancy management

Policy developed by: SA Maternal & Neonatal Clinical Network
Approved SA Health Safety & Quality Strategic Governance Committee on: 19 December 2014
Next review due: 31 December 2017

Summary
Clinical practice guideline on Epilepsy and pregnancy management

Keywords
Epilepsy and pregnancy management, neurological, seizures, antiepileptic, miscarriage, neural tube defects, orofacial defects, congenital, heart, hypospadias, congenital anomalies, hypertelorism, newborn, vomiting, anticonvulsants, mirena, absence seizures, muscle contractions, rash, breastfed, breastfeeding, lamotrigine, confused, headache, bladder control, clinical guideline

Policy history
Is this a new policy? N
Does this policy amend or update an existing policy? Y
Does this policy replace an existing policy? Y
If so, which policies? Epilepsy and pregnancy management

Applies to
All SA Health Portfolio
All Department for Health and Ageing Divisions
All Health Networks
CALHN, SALHN, NALHN, CHSALHN, WCHN, SAAS

Staff impact
All Staff, Management, Admin, Students, Volunteers
All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology

PDS reference CG185

Version control and change history

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Note:
This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach.

Information in this statewide guideline is current at the time of publication.

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The clinical material offered in this statewide standard/policy provides a minimum standard, but does not replace or remove clinical judgement or the professional care and duty necessary for each specific patient case. Where care deviates from that indicated in the statewide guideline contemporaneous documentation with explanation must be provided.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

> Discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary,
> Advising consumers of their choice and ensuring informed consent is obtained,
> Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
> Documenting all care in accordance with mandatory and local requirements
### Table 1 - Classification of epileptic seizures according to clinical type

<table>
<thead>
<tr>
<th>Classification</th>
<th>Temporal lobe SPS</th>
<th>Simple partial seizures (SPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial (focal, local) seizures</td>
<td>Temporal lobe SPS are the most common type of SPS</td>
<td>Symptoms can include:</td>
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<tr>
<td></td>
<td></td>
<td>&gt; An ‘epigastric rising sensation’</td>
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<td></td>
<td></td>
<td>&gt; Déjà vu (the feeling of ‘having been here before’) or jamais vu (where familiar things seem new)</td>
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<tr>
<td></td>
<td></td>
<td>&gt; A flashback of memory</td>
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<td></td>
<td></td>
<td>&gt; A sudden, intense feeling of fear or joy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; A funny taste or smell</td>
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<tr>
<td>Frontal lobe SPS can be harder to describe</td>
<td></td>
<td>Some people experience:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; Strange movements</td>
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<tr>
<td></td>
<td></td>
<td>&gt; A feeling of a wave going through the head or body</td>
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<tr>
<td></td>
<td></td>
<td>&gt; Stiffness or jerking of part of the body that might start in one place, for example the face, and spread to other parts of the body</td>
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<tr>
<td>Parietal lobe SPS</td>
<td></td>
<td>Often include strange sensations such as:</td>
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<tr>
<td></td>
<td></td>
<td>&gt; Numbness or tingling</td>
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<td></td>
<td></td>
<td>&gt; Burning sensations or a feeling of heat</td>
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<tr>
<td></td>
<td></td>
<td>&gt; A feeling that part of the body, an arm or leg, is bigger or smaller than they really are</td>
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<tr>
<td>Occipital lobe SPS</td>
<td></td>
<td>Involve visual sensations, such as:</td>
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<td></td>
<td></td>
<td>&gt; Distortion or loss of vision</td>
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<tr>
<td></td>
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<td>&gt; Seeing flashing lights or coloured shapes</td>
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<tr>
<td></td>
<td></td>
<td>&gt; Seeing people or objects that are not there (hallucinations)</td>
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<tr>
<td>Complex partial seizures (CPS)</td>
<td></td>
<td>Most common CPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; Automatisms such as lip-smacking or chewing movements, or rubbing, stroking or fiddling with their hands;</td>
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<tr>
<td></td>
<td></td>
<td>&gt; Or looking from one side to another in a confused way</td>
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<tr>
<td>Temporal lobe CPS</td>
<td></td>
<td>Often much shorter than temporal lobe CPS, usually lasting about 15-30 seconds:</td>
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<tr>
<td></td>
<td></td>
<td>&gt; Make strange postures with their arms or legs; or</td>
</tr>
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<td></td>
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<td>&gt; Make juddering movements</td>
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### Generalised seizures (convulsive or non convulsive)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tr>
<td>Tonic-clonic seizures</td>
<td>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.</td>
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<tr>
<td>Clonic seizures</td>
<td>A series of myoclonic contractions that regularly recur at a rate of 0.2 – 5/second.</td>
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<td>Atonic seizures</td>
<td>Cause a loss of postural tone. The result is loss of posture (head drops, falls) and are often preceded by a short myoclonic seizure.</td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>Short muscle contractions, usually lasting &lt; 400 milliseconds.</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>Impairment of consciousness alone or with: mild clonic, atonic or tonic components, automatisms and/or autoimmune symptoms or signs.</td>
</tr>
</tbody>
</table>

### Secondarily generalized seizures

<table>
<thead>
<tr>
<th>Partial seizures evolving to secondary generalized seizures (may be generalized tonic-clonic, tonic or clonic)</th>
<th>SPS evolving to generalized seizures</th>
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</thead>
<tbody>
<tr>
<td>CPS evolving to generalized seizures</td>
<td>SPS evolving to CPS and then evolving to generalized seizures</td>
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### Unclassified seizures

Epilepsy

> Epilepsy is a common neurological condition characterised by seizures\(^1\)
> Epileptic seizures are caused by paroxysmal discharges of excessive and/or hypersynchronous abnormal activity of cerebral cortical neurones
> Drug use to control epilepsy in the population ranges from 4 to 9 per 1,000\(^2\)
> 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\(^3\)

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\(^7\)
> Pregnant women with untreated epilepsy are not at increased risk of having a baby with a birth defect\(^8,9\)

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)
Conception

- Pre-pregnancy counselling should provide a clear understanding of the risks of uncontrolled seizures and the possible teratogenicity of anticonvulsant agents
  - For women taking sodium valproate pre-pregnancy, consideration should be given to a suitable alternative agent if appropriate
- Most experts currently recommend high dose folic acid for women taking antiepileptic medication i.e. 5mg / day (10 times the prophylactic dose) for 1 month before conception and continue during the first trimester
- 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:
  - Carbamazepine *(ADEC Cat D)*
  - Clonazepam *(ADEC Cat C)*
  - Ethosuximide *(ADEC Cat D)*
  - Phenobarbitone *(ADEC Cat D)*
  - Phenytoin *(ADEC Cat D)*
  - Primidone *(ADEC Cat D)*
  - Sodium valproate *(ADEC Cat D)*
  - Sulthiame *(ADEC Cat D)*
> In recent years new antiepileptic drugs have been released
>  > Gabapentin (ADEC Cat B1)
>  > Lacosamide (ADEC Cat B3)
>  > Lamotrigine (ADEC Cat D)
>  > Levetiracetam (ADEC Cat B3)
>  > Oxcarbazepine (ADEC Cat D)
>  > Pregabalin (ADEC Cat B3)
>  > Tiagabine (ADEC Cat B3)
>  > Topiramate (ADEC Cat D)
>  > Vigabatrin (ADEC Cat D)
>  > Zonisamide (ADEC Cat D)
> > The following drugs are enzyme-inducing antiepileptic drugs
>  > Carbamazepine
>  > Oxcarbazepine
>  > Phenobarbitone
>  > Phenytoin
>  > Primidone
>  > Topiramate

Phenytoin
>  > Narrow therapeutic window
>  > Increased clearance rate during pregnancy, leading to decreased serum concentrations
>  > Fall in total serum phenytoin concentrations may lead to poor seizure control
>  > Consideration should be given to monitoring phenytoin levels\(^{14}\) (Harden et al. 2009)
>  > Associated major malformations are facial clefts, congenital heart defects and urogenital defects
>  > Associated with Fetal Hydantoin Syndrome (FHS) in 10 % of exposed fetuses (dysmorphic facies and other features, distal phalangeal hypoplasia, abnormal growth and mental / motor development)\(^{15}\)
**Carbamazepine**

> Large peak-trough fluctuations can be minimised by using a controlled-release formulation\(^1\), but this may require higher doses
> Pregnancy may cause a small decrease in the concentration of carbamazepine; consideration should be given to monitoring levels\(^1\)
> Associated with major malformations including neural tube defects in up to 1% of exposed pregnancies, heart defects, inguinal hernia, hypospadias and hip dislocations
> Craniofacial abnormalities and developmental delay have been associated in some but not all studies with the use of carbamazepine both alone or with other anticonvulsants\(^1\)

**Sodium valproate**

> Divided doses are preferred to avoid high peaks in serum concentrations
> Therapeutic range not closely correlated with efficacy – drug level monitoring is of limited value apart from suspected toxicity or non-compliance
> 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
> Large studies have produced an estimate of the incidence of congenital malformations in children exposed to valproic acid during pregnancy ranging from 5 to 18%\(^1\)
> Emerging evidence suggests that valproate exposure in pregnancy may lead to neurodevelopmental delay (including decreased mental development, intelligence quotient (IQ) and cognition, and autism spectrum disorder)\(^1\)

**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

**Lamotrigine**

> Lamotrigine clearance may be increased in pregnancy, leading to a reduction in lamotrigine concentrations and potential loss of seizure control\(^1\)
> Lamotrigine levels should be monitored in pregnancy and the dose adjusted accordingly\(^1\)
> To date data suggest that lamotrigine has not been shown to increase the risk of major birth defects, however there are conflicting reports of an association with the increased risk of oral facial clefts\(^1\)
New antiepileptic drugs

- Gabapentin, lamotrigine, levetiracetam and vigabatrin have no antifolate effects
- To date there has been no evidence of an increased incidence of major malformations with most of the newer antiepileptic drugs, although data are limited
- Topiramate has been changed from ADEC category B3 to category D after inconsistent reports of an increased risk in facial clefts

Management

- The management of seizure activity is covered in PPG, Seizures in Pregnancy

Antenatal

- Physician / neurology review in each trimester
- Document history of seizure activity
- Maternal serum screening for alpha-fetoprotein at 14 – 20 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

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 (see management in seizures in pregnancy)
> 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 (see management of seizures in seizures in pregnancy)

**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 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
  > 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 dysmorphology
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
- If the mother is using antiepileptic drugs that are associated with drowsiness, monitor the breastfed baby for prolonged sedation, disinterest in feeding and inadequate weight gain, and ensure the mother is informed of safe sleeping practices

  > **Lamotrigine requires caution** – If a rash occurs in the baby, breastfeeding should be ceased and the cause of the rash urgently established.

  > For further information regarding antiepileptic drugs in breastfeeding contact the WCHN Medicines and Drug Information Centre – 08 8161 7222 Mon-Fri

**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
  > Topiramate

  > 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
Epilepsy and pregnancy management

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References

2. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052 922 and age-specific fertility rates of women with epilepsy (Level III-2).
15. REPROTOX – Micromedex® Thomson Reuters (Healthcare) Inc. Vol 154, exp 12/2012
Useful web sites
The Australian Pregnancy Register of Antiepileptic Drugs for Women in Pregnancy with Epilepsy and Allied Conditions

International League against Epilepsy (ILEA). Available from URL: http://www.ilae.org/

Abbreviations

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<tr>
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<td>ADEC</td>
<td>Australian Drug Evaluation Committee</td>
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<tr>
<td>AEDs</td>
<td>Anti epileptic drugs</td>
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<tr>
<td>AMH</td>
<td>Australian Medicines Handbook</td>
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<tr>
<td>Cat</td>
<td>Category</td>
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<td>CPS</td>
<td>Complex partial seizures</td>
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<tr>
<td>CYWHS</td>
<td>Children youth and Women’s Health Service</td>
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<td>e.g.</td>
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<td>Et al.</td>
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<td>Fetal Hydantoin Syndrome</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>IUD</td>
<td>Intrauterine device</td>
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<tr>
<td>Kg</td>
<td>Kilograms(s)</td>
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<tr>
<td>Mg</td>
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<td>SPS</td>
<td>Simple partial seizures</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<td>WCHN</td>
<td>Women’s and Children’s Hospital Network</td>
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