Valproate and Women

This is an important brochure, and you (or your legal guardian, if appointed) will need to read, and ask questions on it, so it is fully understood. You (or your legal guardian) will be required to sign to say you / they legally understand this information. We want to ensure you fully understand this information because:

1. As a woman of childbearing age, we want to ensure you, your partner/s and carers understand the risks associated with valproate use during pregnancy.
2. Decisions to take valproate requires you (and your legal guardian, if relevant) and your treating doctor to make important decisions together, to ensure the best care for both you and your unborn child.

If English is not the preferred language for you or your legal guardian, we can arrange for an Interpreter to help you understand the content of this brochure. Further discussions with you will be organised when an Interpreter is available.

Valproate use in pregnant women and women of childbearing potential

You are using valproate. Valproate is a highly effective anti-epileptic drug that has been used in Australia for almost 50 years. However, if you use valproate while pregnant there is a higher risk of causing abnormalities to your unborn child, compared with other anti-epileptic drugs. It is also important to note that the majority of babies born to mothers on a low or average dose of valproate will be normal.

Preferably, valproate should not be taken by a girl or woman who could become pregnant, unless there is no other anti-epileptic drug suitable for that patient. However, for some women other anti-epileptic drugs may not be as successful as valproate in treating their epilepsy. It is important your epilepsy is as well controlled as possible during any pregnancy, as seizures have risks for both you and any unborn baby.

As you are of child-bearing age, it is important that you understand the risks of using or not using valproate to both you and your unborn child if you become pregnant. This brochure provides important information about those risks. Please discuss the brochure with your doctor and ask any questions you may have, so you can fully understand the risks to you and any unborn child.

Avoiding pregnancy whilst on Valproate

It would be best to not get pregnant while using valproate and you should use highly effective contraception to reliably avoid pregnancy. Valproate does not affect the use of the contraceptive pill or other methods of contraception such as injectable contraceptives, intrauterine devices and using a male or female condom or diaphragm.

The most reliable methods include levonorgestrel intrauterine device (Mirena) or progestogen-only implant (Implanon) and 3-monthly injections (Depo Provera), and with these you do not have to remember to take the pill every day or use any barrier methods.

The oral contraceptive pill does not usually interact with valproate however, it must be taken daily (preferably at the same time) to work correctly. Also, if you are sick with vomiting or diarrhoea, or are taking some antibiotics, the oral pill may not work properly.

Barrier methods (such as condoms, diaphragms) are not as reliable as the above methods to prevent pregnancy.

Anti-Epileptic drugs and pregnancy

Most of the information in this section comes from large Pregnancy Registers from around the world. Australia has the **Australian Pregnancy Register for Women on Anti-Epileptic Drugs (APR)** which has been monitoring

women taking anti-epileptic drugs during their pregnancies for 20 years**. You can find information about APR by calling 1800 069 722 or on the web at https://www.neuroscience.org.au/australian-epilepsy-pregnancy-register**

As a general statement, anti-epileptic drugs carry a 4-6% risk of causing birth defects in the unborn child (around 1 baby in 20 is affected) compared to 2-3% risk in healthy women not taking antiepileptic drugs (around 1 baby in 40 is affected). Those risks vary a lot depending on which anti-epileptic drug is used. Taking some anti-epileptic drugs do not have any higher risks compared to women who do not take such drugs.

Of all the epileptic drugs available, valproate has the highest risk of causing abnormalities in an unborn child. The risk is variable according to the daily dose and may range from 5% to more than 20% - the higher the dose, the higher the risk.

If a woman must take an anti-epileptic drug while pregnant, the least risk is to take levetiracetam (Keppra) and lamotrigine (Lamictal), if these drugs can effectively control your seizures. These drugs have risks that are only slightly higher than for women not on anti-epileptic drugs.

Using Valproate while pregnant and the risks to the unborn child

Using valproate while pregnant may cause some or all of the following defects to your unborn child.

1. **Organ and limb abnormalities**
   a) The most common abnormalities in babies whose mothers took valproate involve changes in the heart, penis, and kidneys, and extra fingers or toes. The most serious is spina bifida, where the spine does not develop normally - in severe cases, the child will be unable to walk or control their bladder. Some of these abnormalities may be helped by surgery after the child is born.
   b) The risk of organ and limb abnormalities depends on the dosage of valproate you take.
      i. Valproate doses of 1500 mg per day or more have a risk of about 25% (1 baby out 4 is affected).
      ii. Valproate doses between 700 to 1450 mg/day have a risk of about 10%. (1 baby out of 10 is affected).
      iii. Valproate doses between 500 to 700 mg/day, have a risk of approximately 6.3% (1 baby out of 16 is affected).
      iv. Doses of 500 mg or less per day have a risk of approximately 5% (1 baby out of 20 is affected).
   c) The dose of valproate in the first 12 weeks of pregnancy (the first trimester) is the most critical time as this is when abnormalities are most likely to occur. This is the time when the baby's organs and limbs are being formed.

2. **The baby's intelligence**
   a) If a pregnant woman takes valproate her baby will possibly have lower intelligence. This risk is dependent on the dose taken.
   b) It is not known exactly when during pregnancy this change occurs. It could occur up to 34 weeks during the pregnancy. This means that valproate should be avoided or, if it is essential to take the drug, then the dose should be kept as low as possible throughout pregnancy.

3. **Increase in Autism Spectrum Disorders**
   a) There may be a four-fold increase in autism spectrum disorders in children whose mothers took valproate during pregnancy.
   b) This risk was found with all doses of valproate.
   c) It is not known exactly when during pregnancy this change occurs. It could occur up to 34 weeks during the pregnancy. This means that valproate should be avoided or, if it is essential to take the drug, then the dose should be kept as low as possible throughout pregnancy.
   d) If there is a family history of autism spectrum disorders, there is a higher risk, even without valproate.

Your epilepsy and drug choice

Focal epilepsy:

There are many anti-epileptic drugs which may be as effective as valproate for focal epilepsy.

If you have focal epilepsy, it is recommended you do not use valproate during child-bearing age, as some other drugs carry lower risks to the unborn child when used in pregnancy.

Generalised epilepsy:

a) In women of child-bearing age, with generalised epilepsy, the safest effective anti-epileptic drugs for the unborn child are levetiracetam and lamotrigine.
b) While it is ideal to avoid valproate in women of child-bearing age, sometimes valproate alone or in combination with other drugs may be the only way to properly control seizures.
c) Valproate works well in combination with lamotrigine for women with generalised epilepsies and may allow seizure control with a much lower dose of valproate.
d) If seizures cannot be controlled without using valproate, it is better, where possible, to increase the dose of other drugs, rather than increase the dose of valproate.
e) There is strong evidence that a low dose of valproate (ideally around 200mg/day) in combination with lamotrigine or levetiracetam, has a lower risk for causing abnormalities in the unborn child (compared to a higher dose of valproate on its own).
f) Your doctor will discuss with you what they think may be the best drug combination for you, if you are pregnant or thinking of becoming pregnant.

Reducing the dose of Valproate when planning a pregnancy

If you have a generalised epilepsy, are using valproate and want to become pregnant (or become unexpectedly pregnant), what needs to be done?

Ideally, any change in your treatment should be completed at least 3 months before becoming pregnant, so there is time to see if your epilepsy is controlled. It is important to try to plan your pregnancy and use effective contraception while changing treatment.

If you plan to become pregnant discuss with your doctor the following. If you unexpectedly fall pregnant, you should immediately ask your doctor:

- Is there a need for continuing anti-epileptic drug therapy?
- If you are using valproate, can its dosage be reduced or can you use another anti-epileptic drug, maybe in combination with valproate?
- What other anti-epileptic drugs have been properly trialled for safe use during pregnancy?
- If valproate is essential for your treatment and needs to be continued, is your valproate dose as low as possible?

Any drug dose change needs to be done very carefully and under medical supervision. If changing drug doses, you may have a “breakthrough” seizure which can carry health risks (see below).

There is no general ‘correct’ dose, and it is not possible to know what the lowest effective dose for each person will be in advance of trying different dosages.

The dose required to prevent seizures while pregnant may be reasonably consistent in each person, so information gained in one pregnancy is likely to be helpful in the next.

If medication is changed or your dose reduced:

- Your doctor must tell you about the risks for you, including having recurrent seizures.
- You need to stop driving for at least 3 months. This can be reviewed if seizures are controlled on a lower dose. (See *Assessing Fitness to Drive Guidelines* website below)
  - https://austroads.com.au/__data/assets/pdf_file/0022/104197/AP-G56-17_Assessing_fitness_to_drive_2016_amended_Aug2017.pdf
- There needs to be at least one person with you as much as possible when medication is changed or reduced, due to the risk of seizures. This person must be able to call for medical assistance and assist you in managing a seizure if you have one. Ideally, this includes a person who will stay with you at night-time in case of seizures while you sleep.

Reducing the dose of Valproate imposes risks to both mother and the unborn child

- **Risks to the mother**
  - If valproate is reduced or stopped prior to or during pregnancy, there is a risk that your seizures will become more frequent and in some circumstances unstoppable (called status epilepticus). Two Pregnancy

Registers have shown that 1 in 3 women who stopped valproate during their pregnancy experienced seizures. This is double the rate compared with women who continued valproate (1 in 6 women).
    - If generalised convulsive seizures are poorly controlled, there is a risk of sudden unexpected death during seizures, although that risk is small (0.001% or 1 in 1000 patients each year).
    - Women with epilepsy also have a higher risk of other complications during pregnancy especially if seizures occur. These may include a higher rate of miscarriages, bleeding, and caesarean sections.

- **Risks to** the **Unborn Child**
  If you are pregnant and your seizures are poorly controlled, there may be risks of injury to the unborn child. Those risks include:
    - If you fall while having a seizure you may hurt the unborn child or have a miscarriage.
    - Babies whose mothers experienced seizures during pregnancy may also have an increased risk of low birth weight and premature birth, which could lead to health problems for the baby including learning difficulties.
    - If the mother has a very severe seizure and as a result suffers a lack of oxygen, there is a small risk that the unborn child could die – the unborn child relies on its mother to also provide it with oxygen.

Birth and after birth care

- It is important to have good seizure control for the safety of both the mother and child during and after birth.
- Your body goes through a lot of hormonal and other changes during and after birth. If the dose of valproate has been reduced early in pregnancy, it may need to be increased late in the pregnancy so that seizures do not occur during the birth. Also, the dose of any anti-epileptic drugs which were effective prior to the pregnancy may be inadequate for treating your epilepsy during the pregnancy and doses may need to be increased. After the birth, the dosages (or drug type) may have to be changed.
- After birth is usually a period of a lot of change. With regularly feeding and caring for a baby, many parents don't get enough sleep. This lack of sleep may increase the risk of myoclonic jerks in some women with juvenile myoclonic epilepsy – ask your doctor if this could affect you.
- If you have tonic-clonic seizure or myoclonic jerks, there is a risk that you could drop the baby.
- Breast feeding is positively encouraged for most babies, and the benefits of breastfeeding your baby outweigh any risks.

If you can and wish to breastfeed, speak to your midwife and doctor for advice – for example, maybe your partner could do the night feeds for you, so you can get more sleep.

Further information and resources

Further information and resources are available from Epilepsy Queensland. Their phone number is 07 3435 5000 and website is https://www.epilepsyqueensland.com.au/women-and-epilepsy