

Valproate and Women

1. As a woman of childbearing age, we want to ensure you understand the risks associated with valproate use during pregnancy.
2. The decision to take valproate requires you and your treating doctor to make important decisions together, to ensure the best care for both you and your unborn child.

Key Points

Risks of valproate to the unborn child
<ul style="list-style-type: none">• Organ and limb abnormalities (dose-dependent)• Reduced intelligence (dose-dependent)• Autism spectrum disorder
Risks/consequences of uncontrolled epilepsy in the mother
Risks to the mother
<ul style="list-style-type: none">• Trauma, burns, drowning• Unstoppable seizures• Sudden unexplained death in epilepsy• Inability to drive
Risks to the unborn child
<ul style="list-style-type: none">• Miscarriage• Reduced birth weight• Trauma during the pregnancy

Valproate use in pregnant women and women of childbearing potential

Valproate is a highly effective anti-seizure medicine that has been used in Australia for almost 50 years and is particularly effective for patients with genetic generalised epilepsies – and sometimes can be the only drug that can control the seizures. However, if you use valproate while pregnant there is a higher risk of causing abnormalities to your unborn child, compared with other anti-seizure medicines. 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-seizure drug suitable for that patient that can control her seizures. However, for some women other anti-seizure medicines 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-seizure medicines and pregnancy

Most of the information in this brochure comes from large Pregnancy Registers from around the world. Australia has the **Australian Pregnancy Register for Women on Anti-seizure Medicines (APR)** which has been monitoring women taking anti-seizure medicines 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-seizure medicines 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 medicines (around 1 baby in 40 is affected). Those risks vary a lot depending on which anti-seizure drug is used. Taking some anti-seizure medicines may not have any higher risks compared to women who do not take such medicines, and other newer anti-seizure medicines have not been prescribed to enough women enrolled in pregnancy registers to be certain of their safety.

Of all the anti-seizure medicines available, valproate has the highest risk of causing abnormalities in an unborn child. The risk varies according to the daily dose and ranges from 5% to more than 20% - the higher the dose, the higher the risk.

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

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 (birth defects)

- a) The most common abnormalities in babies whose mothers took valproate involve changes in the heart, penis, face and mouth, and kidneys, and extra fingers or toes. One of 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 of 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 than if she did not take it. This risk is dependent on the dose taken and has not been found when very low doses are used.
- b) It is not known exactly when during pregnancy this change occurs. It could occur up to full term. This means that valproate should be avoided if possible or, if it is necessary to take the drug to control your seizures, 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 full term. This means that valproate should be avoided if possible or, if it is necessary to take the drug to control your seizures, 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-seizure medicines 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 medicines carry lower risks to the unborn child when used in pregnancy. However, for some of the newer medicines, the risk is not yet known.

Generalised epilepsy:

- a) In women of child-bearing age, with generalised epilepsy, the effective anti-seizure medicines with the most established safety record 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 medicines may be the only way to control seizures.
- c) Valproate may work 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 may be better to increase the dose of other medicines, 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-seizure drug therapy?
- If you are using valproate, can its dosage be reduced or can you use another anti-seizure drug instead of or in combination with valproate?
- What other anti-seizure medicines 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 to you and your unborn child (see below).

There is no ‘correct’ dose for all people, and it is not possible to know what the lowest effective dose for each person will be in advance of trying different dosages. Levels in the blood of some medicines may decrease during pregnancy, in particular lamotrigine and levetiracetam, and so higher doses of these medicines may be required to control seizures. Your doctor will commonly monitor your blood levels of these medicines during your pregnancy to assess this.

The dose required to prevent seizures while pregnant may be reasonably consistent for 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 seizures.
- You need to stop driving for at least 3 months, to allow time to see 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 should be 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, severe, 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).
- Seizures may result in injuries, burns and drowning
- If generalised convulsive seizures are poorly controlled, there is a risk of sudden unexpected death during seizures, although that risk is small (approximately 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 injure the unborn child or have a miscarriage.
- Babies whose mothers experience 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 or prolonged 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-seizure medicines 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 seizures.
- 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 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.