

Epilepsy and Women

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Introduction

- Epilepsy can happen to anyone at any time.
- Epilepsies are one of the most common neurological disorders. Approximately 1 percent of the population has epilepsy, making it one of the most common chronic health conditions affecting reproductive-aged women
- Men and women are almost equally affected.

Prevalence

While the prevalence of epilepsy and approach to treatment are similar for men and women, women with epilepsy are more likely to experience seizure patterns that relate to reproductive cycles and are at risk of reproductive health dysfunction and pregnancy complications.

Epilepsy in women

Women bear specific features because of their natural characteristics and changes in hormonal status, which can affect the clinical presentation and the course of the disease as well as the comorbidity of various disorders.

Epilepsy in women

- The association between the menstrual cycle and seizures has been extensively investigated.
- Some research has shown a link between hormones - natural chemicals released by the body - and seizures.
- Thirty to 50 percent of women with epilepsy experience catamenial (menstrual cycle-related) seizures.

Epilepsy in women

The hormones *oestrogen* and *progesterone* are produced in a woman's body from puberty.

- There are times in a woman's life when changes in hormone levels and hormone balance happen:
 - *during her periods,*
 - *during pregnancy*
 - *throughout the menopause.*
- This can have an effect on when epilepsy starts and how often seizures happen. It may also affect when seizures stop.

Hormonal effect on Epilepsy

- These hormones speed up or slow down brain cell activity. This can lower or raise a person's tendency to have seizures.
- The ovarian steroid hormones alter neuronal excitability and affect the seizure threshold.
- Ovarian steroids alter neuronal excitability at the membrane and in the genome.

*Morrell MJ. Epilepsia 1998,
Woolley CS et al. Epilepsia 1998 & J Neurosci 1997*

Epilepsy in women

When *oestrogen* levels are high and when *progesterone* levels are low, some women are more likely to have seizures

Epilepsy in women

- Seizures are more likely to occur near the time of menstrual flow because of progesterone withdrawal and with the estrogen surge at ovulation. For many women, seizures are more random and severe during anovulatory cycles because the ratio of estrogen to progesterone remains high.
- Observations of hormone-seizure relationships have led to interest in hormonal therapies.

Epilepsy in women

Epilepsy and antiepileptic drug-related changes in hypothalamic, pituitary, and gonadal hormones have been associated with:

*increased rates of infertility,
anovulatory cycles,
menstrual irregularity,
polycystic ovaries.*

Puberty

Puberty

Puberty is a common time for epilepsy to start. As changes might also be happening in other areas of life at this time, such as school and friendships, having epilepsy as a teenager can be an added challenge. It can also be a time when young people don't want to feel different from their friends.

Puberty

Anti-epileptic drugs (AEDs) are used to try and stop seizures happening. As with all medication, there is a possibility that AEDs could cause side effects. Some of these side effects could be important to young women as they can cause unwanted changes in appearance and some can delay the start of periods.

Puberty

Perimenarche may be a risk for the development and worsening of epilepsy.

In a study Klein showed that epilepsy began during the year of menarche in 17% of patients vs 5.5% expected ($p < 0.001$).

During +/-2 years of menarche in 38% patients vs 22% expected ($p < 0.001$).

While seizures worsened during perimenarche in 29% of girls with pre-existing epilepsy.

Fertility

Reproductive Dysfunction

- Reproductive dysfunction is reported in women with epilepsy treated with AEDs. In women, the most common symptoms are
 - hyperandrogenism,
 - menstrual disorders with ovulatory failure,
 - polycystic ovary-appearing ovaries or polycystic ovary syndrome, and hyperinsulinemia.
- These symptoms may be secondary to epilepsy or to AED treatment, particularly with valproate

Polycystic ovary syndrome (PCOS)

This syndrome happens when follicles - ova from the ovary - do not develop properly. These ova are usually released every month during a period. For women with PCOS, ova are not released and they stay in the ovary and form cysts. This syndrome also causes a higher level of the hormone testosterone than normal.

Polycystic ovary syndrome (PCOS)

- PCOS can cause
 - irregular or infrequent periods
 - weight gain
 - increased hair growth.
 - It may also make becoming pregnant more difficult

Polycystic ovary syndrome (PCOS)

Valproate, may directly cause PCOS or indirectly lead to the disorder by causing weight gain that triggers insulin resistance, increased testosterone levels, and other reproductive abnormalities

Polycystic ovary syndrome (PCOS)

Polycystic ovarian syndrome is widely believed to be common in women with epilepsy, but the actual prevalence and the pathogenesis of PCOS in this population are disputed.

Contraception

Contraception

There are many different methods of contraception to prevent pregnancy.

There are no contraindications to the use of nonhormonal methods of contraception in women with epilepsy

Barrier methods

Barrier methods of contraception include condoms, diaphragms and caps. These methods are not affected by taking AEDs.

Intrauterine devices (IUDs) and intrauterine systems (IUSs)

- IUCDs (often called 'the coil') are devices that are fitted into the womb.
- The Mirena coil is an IUSs which contains the hormone progesterone (in a slow release form called levonorgestrel). Like barrier methods such as condoms and diaphragms, IUCDs and IUSs are not affected by AEDs.

Contraception

There is no evidence that the contraceptive pill affects epilepsy or AEDs. But some AEDs can affect how well the pill works. This depends on which AED is being taken

Contraception

Some methods of contraception may be **less effective for women taking AEDs** than for women not taking AEDs. This depends on the individual and which AEDs they are taking. AEDs can be divided into two groups, enzyme-inducing drugs and non enzyme-inducing drugs. The AED that is being taken may affect what contraception is chosen.

Contraception

- Non enzyme-inducing AEDs (valproate sodium, benzodiazepines, ethosuximide, and levetiracetam) do not show any interactions with the combined oral contraceptive pill.
- There are interactions between the COCP and hepatic microsomal-inducing AEDs (phenytoin, barbiturates, carbamazepine, topiramate [doses above 200 mg/day], and oxcarbazepine) and also lamotrigine.

The combined oral contraceptive pill - 'the pill'

- Enzyme-inducing AEDs cause the hormones in the pill to be broken down more quickly, so the pill is less effective.
- If a woman is taking an enzyme-inducing AED she may be given the pill with a higher amount of oestrogen. Even with this higher dose, the pill can still be unreliable.
- To be effective it is often best to use other methods of contraception.

The combined oral contraceptive pill - 'the pill'

Usually when a woman's oestrogen levels are high, there is a higher risk of seizures happening. But when the levels of oestrogen are higher because of the pill, the risk of seizures is not higher. This is because the body gets rid of the oestrogen from the pill quickly.

If bleeding happens between periods, it means that the dose of oestrogen is not enough and the pill may not be reliable against becoming pregnant.

Preconception

Starting a family

- Pre-conception counselling
- Risks during pregnancy, associated with epilepsy and anti-epileptic drugs
- Risks of major congenital malformations related to specific anti-epileptic drugs
- Minor congenital abnormalities

Starting a family

Folic acid

- Folic acid supplements of 5mg a day should be taken by women with epilepsy who are planning a family.
- These should start before conception and be continued throughout the first three months of pregnancy.
- As accidental pregnancies are common, some doctors suggest that any woman with epilepsy who could become pregnant should take 5mg of folic acid daily all the time.

Starting a family

Folic acid

There is some evidence, however, that folic acid can interact with phenytoin and primidone, making them less effective.

Pregnancy

Pregnancy

Most pregnancies have a favourable outcome in women with epilepsy, and these women should not be discouraged from becoming pregnant

During pregnancy, the major risks to mother and child result from loss of seizure control on the one hand, and an elevated risk of major congenital malformations due to antiepileptic drug treatment on the other.

Pregnancy

In a community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy compared to 24,778 singleton unaffected controls, Viinikainen K et al from the Department of Neurology, Kuopio University Hospital and University of Kuopio, Kuopio, Finland showed that:

Pregnancy

During pregnancy, the seizure frequency was unchanged, or the change was for the better in the majority (83%) of the patients.

No significant differences between Women With Active Epilepsy and controls in the incidence of preeclampsia, preterm labor, or in the rates of caesarean sections, perinatal mortality, or low birth weight.

Pregnancy

The rate of small-for-gestational-age infants was significantly higher, and the head circumference was significantly smaller in WWAE.

Apgar score at 1 min was lower in children of WWAE, and the need for care in the neonatal ward and neonatal intensive care were increased as compared with controls.

The frequency of major malformations was 4.8% (-0.6-10.2%; 95% confidence interval) in the 127 children of WWAE.

Pregnancy

Children who are born to women with epilepsy have a higher risk of birth defects, probably related to in-utero exposure to antiepileptic drugs.

Because available evidence does not suggest that epilepsy per se is associated with a major increase in the risk of Major Congenital Anomalies (MCA).

Establishing definite evidence of teratogenicity with a particular drug is difficult.

Valproic acid is associated with a greater incidence of MCAs than other AEDs.

Pregnancy

- VPA has been associated with a variety of major and minor malformations, an increase in neural tube defects, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects, and autism.
- Polytherapy treatment in epileptic pregnant women increases the risk of teratogenicity in offspring
- There is an established relationship between VPA dose and adverse outcome.

Pregnancy

- There is some recent evidence to suggest that these drugs may also affect cognitive and behavioural development.
- Developmental delay, characterised by low verbal IQ, has also been reported in children exposed to valproic acid in utero, although the relative risk is not precisely known.

Pregnancy

- Fetal valproate syndrome results from in utero exposure to valproic acid. It is
- Characterized by a distinctive facial appearance, a cluster of minor and major anomalies, and central nervous system dysfunction.

Pregnancy

- Investigations
 - Ultrasound
 - Blood levels especially in women whose epilepsy is normally difficult to control

Pregnancy

These hormone-seizure interactions and reproductive health concerns complicate the management of epilepsy in women.

Once you are pregnant

- Many women will not experience a change to their seizure frequency during pregnancy.
- Some women will have fewer seizures and around a third will have more seizures.
- It is important that a doctor experienced in treating women with epilepsy carefully monitors anti-epileptic drug (AED) levels during pregnancy because the AED levels may decrease and the dosage may need to be increased..

Once you are pregnant

Current evidence suggests that unborn babies are only very rarely harmed by their mothers' seizures, unless the mother falls and injures the baby. For this reason, it is a good idea to aim to have as few seizures as possible during pregnancy.

Giving birth

- Epilepsy should not prevent having a normal labour and delivery.
- Anti-epileptic drugs (AEDs) should be taken as per usual schedule during labour.

Giving birth

- Epidural anaesthesia/analgesia can be used in labour.
- Some doctors feel Pethidine is probably best avoided as this may trigger seizures.
- Entanox, nitrous oxide and oxygen is safe, so long as the mother does not over-breathe when using it, since over-breathing can trigger seizures in some people.

Breast-feeding

- The decision whether to breast-feed is up to the mother. Unless the baby is born prematurely, the small amount of anti-epileptic drug (AED) that gets into breast milk is very unlikely to affect the baby.
- In prematures it is advisable to discuss breast-feeding with your baby's paediatrician, because some AEDs may accumulate in the baby's body and may cause them problems

Menopause

The menopause

The menopause is a time of hormonal upheaval and physical change. Some women develop epilepsy at this time; others see the end of a history of seizures. In common with women without the condition, many women with epilepsy will consider whether hormone replacement therapy (HRT) can be of benefit to them.

The menopause

- The menopause is when a woman's periods stop and she can no longer become pregnant.
- During this time a woman's body stops making natural hormones and she may have symptoms such as hot flushes and changes in mood.
- Hormone replacement therapy (HRT) is sometimes used to help with these symptoms by adding either *oestrogen* or a combination of *oestrogen* and *progesterone*.

The menopause

- Generally when a woman's *oestrogen* levels are high, there is a higher risk of seizures happening.
- The small amount of *oestrogen* in HRT does not usually cause more seizures. If seizures do get worse, it is possible that this could be due to the increased intake of *oestrogen*.

The menopause

- Some women may not wish to use HRT preparations as they can bring with them their own risks.
- Hormones can help with short term symptoms of the menopause such as hot flushes, sweats and dry vagina. They also help protect against brittle bone disease *osteoporosis*. This is especially important as some AEDs affect the body's calcium balance and therefore increase the risk of osteoporosis

Conclusion

Conclusion

To provide the best care for patients with epilepsy, particularly women of reproductive age, clinicians must consider both the gender-based biology of epilepsy and the effects of antiepileptic drugs on reproductive health.

Conclusion

There is a mutual influence of steroid hormones and antiepileptic drugs, calcium and phosphorus transport disorder, insulin and lipid metabolism, adverse cosmetic effects, sexual dysfunctions, pregnancy, teratogenicity and the delay in fetal development and bone diseases.

THANK YOU



Antiepileptic Drug Effects on Oral Contraceptives

- **Agents that induce liver enzymes and may compromise Oral Contraceptive efficacy**
 - Carbamazepine
 - Felbamate
 - Phenytoin
 - Phenobarbital
 - Primidone
 - Oxcarbazepine
 - Topiramate
- **Agents that do not compromise Oral Contraceptive efficacy**
 - Gabapentin
 - Levetiracetam
 - Lamotrigine
 - Tiagabine
 - Valproate
 - Zonisamide

Menstrual cycles and periods

Thirty percent of women with epilepsy find that their seizures are affected by their periods. This might be due to the changes in the hormones that happen during their menstrual cycle.

Some women find their seizures often happen just before and during their period. Others may find their seizures regularly occur at another particular time during their cycle, such as at mid cycle (ovulation)

Menstrual cycles and periods

When women have seizures only during their periods and at no other time, this is called *catamenial* epilepsy. Women with catamenial epilepsy might benefit from taking an extra type of medication during the week before and for the first few days of their period.