

WOMEN AND EPILEPSY

Women and epilepsy: Reproductive life and epilepsy

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The management of women with epilepsy (WWE) presents a number of gender specific issues related to the reproductive cycle including, cosmetic adverse effects of the antiepileptic drugs (AEDs), menstrual changes in seizure frequency, interaction between AEDs and oral contraceptives, fertility, reproductive and endocrine disturbances, pregnancy and bone metabolism.¹

Cosmetic effects of AEDs

Cosmetic effects of AEDs are of particular concern to the female population. Weight gain is particularly common with valproate and is more common in women than in men. Hair loss and hair regrowth occur with valproate and phenytoin is associated with excessive hair growth and gingival hypertrophy.

Catamenial epilepsy and menopause and epilepsy

Menstrual exacerbation of seizure frequency (catamenial epilepsy) is common and thought to relate to high oestrogen and low progesterone levels. Up to one-half of WWE report variation in seizure frequency with their menstrual cycle. The time of seizure exacerbation varies but most commonly occurs just before and during menstruation and at the time of ovulation. It may be more evident with anovulatory cycles, during which oestrogen levels remain high and progesterone levels remain low. The effect of menopause and the perimenopause and hormone replacement therapy on seizure frequency has not been extensively studied, but in some women there is a significant change in seizure frequency.

Oral contraceptives and AEDs

Contraceptive failure is higher in women receiving cytochrome P450 enzyme inducing drugs and oral hormone contraceptives, due to increasing metabolism and binding of contraceptive steroids. There is no evidence that oral contraceptive hormones increase seizure frequency.

Fertility

Fertility rates in WWE are estimated to be one-third of the general female population. This is thought to relate to a number of factors including the effect of seizure activity and epileptic discharges on pituitary and hypothalamic function influencing ovulation, increased prolactin levels, increase in anovulatory cycles, increased incidence of polycystic ovaries, sexual dysfunction, the effect of AEDs on reproductive and endocrine function, social pressure not to have children and associated discrimination. Women with partial or focal epilepsies have higher rates of infertility than women with generalized epilepsies. Up to one-third of women with temporal lobe epilepsy have been reported to have anovulatory cycles compared with 10% of the general population and women with primary generalized epilepsy. Reproductive endocrine dysfunction is thought to be common in WWE. These women have steroid hormone abnormalities related to AEDs. Oestrogen, progesterone and testosterone are metabolized by the cytochrome P450 enzyme system. Enzyme inducing AEDs increase the metabolism and hence reduce plasma concentrations of both gonadal and adrenal steroid hormones. In addition these AEDs promote binding of steroids, reducing the bioavailable fraction of the steroid hormone. Valproate inhibits the cytochrome P450 enzymes, reducing metabolism and increasing levels. A condition similar to polycystic ovaries with multiple ovarian cysts, menstrual irregularities and hyperandrogenism has been described in up to 40% of WWE, particularly those treated with valproate. This condition may relate to obesity associated with this drug.

Pregnancy

Pregnancy in WWE is associated with a risk of increase in seizure frequency, higher risk of miscarriage and complications in labour, and a greater risk of adverse outcome. During pregnancy one-third of women have an increase in seizure

frequency. There appear to be no predictive factors. Possible causes include increase in oestrogen levels, altered AEDs prior to pregnancy in an attempt to reduce teratogenicity and a decline in plasma AED levels during pregnancy. Reduction in plasma levels is thought to be multifactorial, including increased clearance, reduced protein binding, increase in maternal weight and poor drug compliance.

Most WVE taking AEDs during pregnancy have a higher risk of congenital malformations, microcephaly and neurocognitive effects. As a result of methodological and case ascertainment differences, the estimates of this risk vary widely between the various studies. Prospective data regarding relative risk of different AEDs, drug combinations and doses has been lacking. Furthermore, the number of types of AEDs on the market has been rapidly increasing over the past decade, and for most of the new drugs there is inadequate information regarding safety in pregnancy. As a result, clear practice guidelines for the treatment of women who may become pregnant have been difficult to formulate. Recently large-scale, prospective, broad-based studies have been established which are now starting to release information that is of major relevance to clinical practice.^{2,3} The most important finding to come out of *The Australian Registry of Pregnancies Exposed to Antiepileptic Drugs* is a dose effect for valproate treatment. For women taking valproate during the first trimester (>1,100 mg) there is a significantly increased risk of congenital malformations in the foetus. Folate supplementation was not found to be protective against AED induced congenital malformations, despite the evidence for its effect in reducing the incidence of neural tube defects in "high risk" populations and the general community.⁴ All women on AEDs planning a pregnancy should be advised to take folate supplements. Evidence for the relative risk for congenital malformations of AEDs other than valproate requires more women to be enrolled. The potential risk of AED exposure during pregnancy for the long-term neurocognitive outcome in the child remains unknown.

Breastfeeding

All the AEDs are present in breast milk, although the relative levels (compared to plasma) of the different drugs varies greatly in inverse proportion to their protein binding. Despite this there is no evidence of harmful effects on the infant although well-conducted studies are lacking.

Bone metabolism

Patients taking AEDs have high rates of bone fractures. A recent case-control study of 231,778 adult patients (52.5% females) from the UK General Practice Research Database found that use of AEDs had the highest odds-ratio for fracture of all independent risk factors assessed.⁵ The basis for this strong association of AED use with fracture risk is likely multifactorial. It may include increased bone fragility and AED-induced falls risk, as well as a direct effect of trauma from the seizures. While osteoporosis can affect both sexes, the problem is particularly prevalent in older women.

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