Epilepsy and anti-epileptic drugs (AEDs) have complex interactions with hormones and the functioning of the hypothalamic pituitary axis. This complexity can result in reproductive endocrine dysfunction in up to 30 percent of women with epilepsy (WWE). For example, estrogen has been demonstrated to have proconvulsant effects via both a short latency, short-acting membrane effect and a long latency genomic effect. Conversely, progesterone has been demonstrated to have an inhibitory effect via enhancement of GABA channel function. Effects on female reproductive health can include menstrual cycle abnormalities, anovulatory cycles, sexual dysfunction, infertility, polycystic ovarian syndrome and premature ovarian failure. These disorders are hypothesized to result from mechanisms resulting in disruption of the hypothalamic pituitary axis by seizures and/or interictal discharges as well as interactions of AEDs with ovarian steroid hormones.

**DISRUPTION OF THE HYPOTHALAMIC-PITUITARY AXIS**

Reproductive dysfunction has been reported in patients with epilepsy in the absence of use of AEDs. Gonadotrophic-releasing hormone (GnRH) is released by the hypothalamus in a pulsatile manner which stimulates the release of the gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland. Epilepsy can be an endocrine disruptor and alter the levels of GnRH, LH, FSH, and prolactin with downstream effect on levels of estrogen, progesterone and testosterone in WWE. This effect is thought to result from significant connectivity of the hypothalamic pituitary axis with the limbic system. Generalized seizures and/or interictal discharges disrupt the pulsatile secretion of GnRH resulting in increases in LH and FSH in WWE. WWE have been found to have high levels of LH and altered LH to FSH ratio and elevated prolactin levels. These hormonal changes can lead to irregular menses, anovulatory cycles and premature menopause.

**AED EFFECTS ON REPRODUCTIVE FUNCTION**

AEDs that induce hepatic cytochrome P450 3A4 isoenzymes, such as phenobarbital, phenytoin, and carbamazepine, result in decreased levels of estrogens and androgens including testosterone, as they are also substrates for this isoenzyme system. These AEDs are also found to result in elevations in sex hormone binding globulin (SHBG). The combination of these two factors results in a reduction in the amount of biologically active serum hormone levels resulting in menstrual disorders and anovulation.

AEDs that are inhibitors of cytochrome P450 2C9 and 2C19 isoenzymes, such as valproate, result in higher testosterone and androgen levels contributing to the development of PCOS. PCOS or a hyperandrogenic state is thought to arise in the presence of valproate via inhibition of normal ovarian hormone production resulting in a non-ovulatory follicle that produces testosterone.

**POLYCYSTIC OVARIAN SYNDROME (PCOS)**

PCOS affects seven percent women in the childbearing age. WWE appear to be at an increased risk of developing PCOS, which occurs in 10-25 percent of WWE. PCOS is defined by both phenotypic and serologic characteristics with polycystic appearing ovaries, hyperandrogenism, hirsutism, acne, insulin resistance and increased LH/FSH ratio. The elevated LH/FSH ratio produces follicles that do not fully mature, but become numerous and cystic. These follicles primarily produce androgens, as they lack aromatase, the enzyme responsible for the conversion of testosterone to estrogen. This effect is worsened by the conversion of androgens to estrogen by aromatase in the periphery, resulting in elevated circulating estrogen with feedback to the pituitary and dysregulation of LH secretion. As noted above, increased LH to FSH ratio has been found in women with IGE and localization related epilepsy (LRE), with the ratio being higher in women with IGE thought due to use of valproate in these women. Women with IGE taking VPA have a higher risk of anovulatory cycles and developing PCOS. VPA has been
implicated in the development of PCOS occurring in some studies in up to 40 percent of women.5 Valproate inhibits aromatase, inhibits insulin metabolism, with higher circulating levels, causing insulin resistance and weight gain.1 PCOS was more likely if VPA was initiated before the age of 20 years.2

**PREMATURE OVARIAN FAILURE**

WWE have a higher likelihood of earlier menopause, which is postulated to be due to hypothalamic-pituitary-gonadal axis dysfunction with early loss of follicles available for ovulation.1 In one study, 14 percent of WWE with epilepsy were reported to have premature ovarian failure as compared to four percent on the general population.6 Women with frequent seizures have been reported to have an earlier menopause.7

**INFERTILITY**

As the above discussion would imply, fertility is also affected in WWE by as much as two thirds of expected though estimates of the effect vary.1,4,5,8 The cause of lower rates of fertility in WWE are multifactorial, including social factors and biological factors. Social factors include: not having children by choice due to the fear of inheritance of epilepsy in the off-spring, concern for risk of fetal malformations and difficulties encountered in caring for a child if the mother has seizures. Biologic factors include effects of AEDs on reproductive hormones, menstrual dysfunction and anovulatory cycles, PCOS, decreased sexual interest and premature ovarian failure.1,2 The other important predictors of infertility are being on polytherapy, particularly three or more drugs, older age and low education. Phenobarbital, either as monotherapy or polytherapy is more likely to be associated with infertility due to its enzyme inducing properties.8

**SEXUAL DYSFUNCTION**

People with epilepsy have been reported to have a higher incidence of sexual dysfunction than the general population. It has been reported to occur in 30-66 percent of men and 14-50 percent of women with epilepsy.9 Multiple factors have been thought to be contributing factors, including the effect of epilepsy, comorbid depression, effects of AEDs and psychosocial factors including relationship with the partner, poor self-esteem and sexual self-image, feeling sexually unattractive and cultural factors.3,5 Sexual dysfunction in people with epilepsy may be caused by alterations in the pituitary gonadotrophins, prolactin and sex steroid hormones. Reductions in LH, elevated prolactin, and low testosterone levels have been found to be associated with sexual dysfunction in people with epilepsy. AEDs, particularly the enzyme inducing AEDs also contribute to sexual dysfunction with decreased estrogen and testosterone levels.3,5 More than a third of WWE report decreased vaginal lubrication, dyspareunia and vaginismus.5 Women with IGE were more likely to have anorgasmia and sexual dissatisfaction as compared to women with LRE who were more likely to have sexual anxiety, dyspareunia and vaginismus.5 People with temporal lobe epilepsy (TLE) have higher incidence of sexual dysfunction as compared to people with IGE, with men with TLE having a decreased testosterone/LH ratio.3 Women with right TLE are more likely to have sexual dysfunction with decreased sexual interest and hyposexuality as a result of hypogonadotrophic hypogonadism as compared to women with left TLE.2 Patients undergoing right temporal lobe surgery for drug resistant epilepsy were more likely to have improvement in sexual function occurring in 79 percent as compared to 53 percent in those undergoing left temporal lobe surgery.3

**CONCLUSION**

Certainly more research is needed into the complex interactions between epilepsy and reproductive function. Specific patients may have enhanced vulnerability to certain disorders of reproductive function based on the specific epilepsy type, the combination of AEDs used to treat her epilepsy, seizure frequency, and personal hormonal milieu.1 For example, women with focal epilepsies, particularly temporal lobe epilepsy have a higher incidence of reproductive dysfunction as compared to women with generalized epilepsy; left sided discharges have been more closely associated with PCOS; right sided discharges are more commonly associated with hypogonadotrophic hypogonadism; menstrual disorders have been more commonly reported in women with a higher seizure frequency.1,2 In order to better detect and diagnose disorders of reproductive function associated with epilepsy providers should actively solicit history related to hormonal and reproductive health as WWE may be hesitant to share this history or unaware of the relationship between epilepsy and reproductive function. Evaluation should include a general and neurologic history and physical, hormone levels (LH, FSH, estrogen, progesterone, prolactin and testosterone), and gynecologic consultation when a reproductive endocrine disorder is suspected.5 Evaluation of the possible contribution of AEDs on reproductive endocrine dysfunction is essential in that dysfunction due to effects of AEDs may be modified or reversed with selection of an alternate agent for seizure control such as the substitution of carbamazepine with a non-inducing agent.1,2

---