The Effects of Epilepsy and Its Treatment on Sexual and Reproductive Functions

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The quality of human life is a summation of many factors. Male and female sexuality, relationships and successful reproduction are paramount in the accomplishment of a meaningful life for most individuals. Evaluation of these measures for our patients with epilepsy has revealed a disparity between their experience and that of the general population. Human sexuality is a psychological and physiological experience. To understand the problems our patients encounter, we will briefly review the human hormonal sexual system and what is altered in the experience of the individual with epilepsy.

Steroids are hormones that are released into the circulation. At target tissue membranes they are taken into the cell and bind to an intracellular cytosolic receptor. This complex is then transported into the nucleus and binds to DNA, which results in increased RNA polymerase activity and eventual polypeptide formation. These are long latency effects. Steroids have short latency effects also.[1] (Table 1)

Long Latency and Duration – Hours/Days
Cytoplasmic receptor binding **Intranuclear DNA receptor binding** **Alter genomic transcription and translation** **Post-transcriptional protein synthesis** **CA-1 dendritic spines and excitatory synapses**
Short Latency and Duration – Seconds/Minutes
Allosteric effects on ion channel conduction via recognition site

Table 1. Steroid Effects[1]

Female Sexual Function

The sexual steroids are 17-B steroids. The primary female compounds are estrogen and progesterone. (Figure 1) The male major androgen is testosterone. The major production of

these compounds occurs in the sexual glands, but they are also formed in the adrenals and in the brain. In human brain there is active interconversion between androgens and estrogen. The 17-B steroid reductase and dihydrogenase are found in temporal lobe. The concentration is greater in subcortical white matter than in cortex.[2] Figure 1 outlines the feedback systems between the CNS and the sexual end organ.

Progesterone and its metabolites induce anesthesia and are sedative. (Table 2) In human female brains at autopsy, progesterone levels are higher in the amygdala and cortex than in other brain regions. The concentrations are greater in fertile women than in postmenopausal women.[3] In the rat progesterone levels are high in the forebrain neocortex and decrease in puberty. The 5-alpha reductase that metabolizes progesterone to 5-alpha dihydroprogesterone (5-alpha DHP) is found in neurons. The 3-alpha dihydrogenase that further metabolizes 5-alpha DHP to allopregnanolone is in astrocytes.[3] Progesterone retards the kindling in rat amygdala and dorsal hippocampus and blocks behavioral seizures in fully kindled female rats.[4] Progesterone has an identified binding site on the GABA-A receptor.[3] (Table 3)

Estradiol	Progesterone	Testosterone
Elation	Depression	Either
Anxiety	Sedation	Either
Lability	Stability	Impulsive, Aggressive
Anorexia	Weight Gain	Sleep Apnea
Insomnia	Hypnosis	Anabolic

Table 2. Behavior and Sex Steroids[13]

Neurotransmitter Effects	Neurophysiological Effects
GABA-A Receptor Recognition	Inhibit Kindling

Site	
Potentiate Adenosine Inhibition	**Decrease Interictal Spike Frequency**
Neuroprotective	**Increase Threshold: Electroconvulsive & Chemical Seizures**

Table 3. Progesterone in CNS[13,15]

Estrogen receptors are predominant in the cortex and regress with puberty in pre-pubertal rats. Estrogen produces insomnia and decreased appetite. (Table 2) In the mature rat, estrogen receptors are greatest in the limbic cortex in the medial amygdala and lateral septal nuclei, as well as in the medial preoptic and medial hypothalamic regions.[3] Kindling in the amygdala and in the dorsal hippocampus occurs more quickly in the presence of estrogen. Afterdischarge threshold in the amygdala is lowest at pre-ovulation and menstruation, a time when the estradiol:progesterone ratio is the highest. Stimulating the amygdala produces ovulation, while ablation of the amygdala results in decreased sex drive, change in lutenizing hormone (LH) pulsatility, and change in the estrus cycle in the rat. Stimulation of the mesial temporal region produces up to a five-times elevation in prolactin.[5] Estrogen induces cortical excitability. (Table 4)

Neurotransmitter Effects	Neurophysiological Effects
Potentiate Glutamate-NMDA in CA-1	**↑ CA-1 Dendritic Spines & Excitatory Synapses**
Block GABA Mediated Transmission	**↑ Neuronal Firing Rates & Spontaneous Discharges**
↓Chloride Conductance	**Activate EEG and Produce Seizures**
Alter GAD	**Reduce Electroconvulsive Shock Threshold**
↓ Synthesis Rate GABA-A Subunits	**Create Epileptic Focus with Topical Application**

↑ Monoamine Levels	**↑ Severity and Duration of Chemical Models**
↑ Serotonin Synthesis	

Table 4. Estrogen/Estradiol in CNS[13,15]

Female rats fully kindled from the basolateral amygdala were found to have high estradiol levels, high prolactin levels, and poly-follicular ovaries. Estrous cycles were disrupted even before kindling was completed in some rats. These rats failed to respond to progesterone supplementation; this implicates a failure of the hypothalamic-pituitary axis. The excessive neural activity and the prolonged elevated estradiol exposure was felt to produce the axonal degeneration seen in the arcuate nucleus of the hypothalamus. In the hypothalamus, the sensitivity to ovarian steroids was altered, as well as the catecholamine-adrenergic regulation of the suprachiasmatic nucleus. These findings result in a net loss of reproductive cyclicity in the rats.[5] In animal experiments, stimulating the amygdala produces ovulation; ablating it results in decreased sex drive, change in LH pulsatility and change in the estrous cycle. Stimulation of mesial temporal region produces up to a five times elevation in prolactin.

Effects of Epilepsy and Treatment on Female Sexual Function

At puberty, the female develops a cyclical pattern of serum estrogen and progesterone production from the mature ovary resulting in luteal and follicular stages.[6] A cycle in which ovulation does not occur has an inadequate luteal phase hallmarked by a progesterone level of less than 5 ng/ml. The estrogen:progesterone ratio is highest at ovulation and menstruation and lowest in the luteal phase. The finding that progesterone is greatest in the temporal cortex

of a fertile women[3] may lead to a speculation that falling progesterone levels or an increased ratio of estrogen:progesterone may result in increased seizure occurrence in some women relative to their menstrual cycle, i.e., catamenial epilepsy.

In women with epilepsy, 30-50% have predictable patterns of seizure occurrence at various times in the menstrual cycle. (Figure 2) The C1 pattern is seen in 70% and occurs in the perimenstrual time when estrogen and progesterone are high. The C2 pattern occurs at the ovulatory peak of estrogen. The C3 pattern is a broad-based pattern reflecting an inadequate luteal phase.[6] Attempts to improve seizure control in women with these patterns has centered on manipulation of progesterone or estrogen levels. (Table 5) Oral progesterone is nearly completely metabolized on first pass. Natural and synthetic oral progestins and synthetic medroxyprogesterone injections have been used, producing seizure reductions of 62-68%.[7-10] Clomiphene is an estrogen antagonist that induces ovulatory cycles. When used in women with partial seizures and menstrual disorders, 10 of 12 women experienced an improvement of 87%.[12]

Regimen	Number of Patients	Months in Study	Percent*
Depomedroxyprogesterone 120-150 mg IM q6-12 wk			
Depomedroxyprogesterone 400 mg IM weekly	**1**	**4**	**90%**
Medroxyprogesterone 5-10 mg PO da 15-18	**24**	**3**	**42%**
Progesterone 100-200 mg PO tid, da 15-28	**25**	**3**	**72%**
	15+	**36**	**100%**

Progesterone 100-200 mg PR, da 15-28	**8**	**3**	**74%**
Clomiphene	**12**		**87%**

*** percent of group who had significant decrease in seizures**
+ long term follow up of responders from prior group of 25

Table 5. Hormonal Treatment in Catamenial Epilepsy[7-13]

Fifty percent of women with epilepsy have menstrual dysfunction, 20% being amenorrheic.[13] Anovulatory cycles are found in up to 35%, compared to 8% in a control group of normal females. This appears to be a greater problem in temporal lobe epilepsy in some reports.[14] Most anovulatory cycles are seen in women who have polycystic ovaries, but who do not express the full syndrome[15] (increased body-mass index, hyperandrogenism, hair loss and polycystic ovaries[16]). These abnormalities are seen in women with epilepsy who are not on AED (anti-epileptic drug) treatment as well as those on AEDs. In a control population of normal women without epilepsy 18% had polycystic ovaries and 16% of these had irregular cycles; if the women had menstrual disorders, 88% had polycystic ovaries. If women with epilepsy on AEDs had menstrual disturbance, polycystic ovaries were seen in 42%; if menses were regular, 20% had polycystic ovaries.[17]

Murialdo[15] evaluated adult women with idiopathic generalized seizures and partial epilepsy of temporal and extratemporal origin, both uncontrolled and controlled.[13] Menstrual irregularity was present in 22%. Luteal deficiency was seen in 38% of whom 80% were on valproate. Anovulation occurred in 29% and polycystic ovaries were seen on ultrasound in 46% of those who had ultrasound. In another series of 238 women with epilepsy, 80% of the women who had received valproate before age 20 had polycystic ovaries or hyperandrogenism.[17]

Vainionpaa evaluated 78 prepubertal to postpubertal females; 41 on valproate, 19 on carbamazepine and 18 on oxcarbazepine. None of the individuals had other brain damage. Valproate therapy had been ongoing from 0.8 to 10.3 years in these females eight to 18 years of age. Forty-four percent had hyperandrogenism. Polycystic ovaries were found in seven of 14 by ultrasound, compared to five of 16 controls. Hyperandrogenism was seen in one-third of prepubertal and pubertal girls and one-half of postpubertal girls with epilepsy. Three of four postpubertal girls with epilepsy who had menstrual abnormalities had hyperandrogenism. Obesity did not correlate with hyperandrogenism, nor did hyperinsulinemia.[18] In adult women, a change from valproate to lamotrigine reversed the hyperandrogenism.[15]

Menarche exacerbates seizures in 37% of pubertal girls, especially if the seizures are localization-related.[19] Women may have changes in seizure frequency with menopause, but the effects are variable and unpredictable: 30-40% worsening, 30-40% improving, and 30% having no change.[20,21] Questionnaires returned by perimenopausal and menopausal women reported that if a catamenial pattern was present before menopause, 68% of these women had decreased seizures at menopause. If there was no catamenial pattern, the course of postmenopausal women was variable. Hormone replacement therapy in these women increased the risk of increased seizures at menopause in 60% of the women given hormonal replacement therapy. Of those patients who did not have hormonal replacement therapy, only three of the 26 patients had an increase in seizures at menopause.[21]

Clinical Care of Women with Epilepsy

The survival of the species depends on successful reproduction. Most (90%) pregnancies in women with epilepsy are normal. Women with epilepsy are at risk for decreased reproductive function and unsuccessful pregnancy outcomes. Considerable effort has been made in the past several years to disseminate information to consumers and professionals in order to improve women's health, fetal health, and successful deliveries of healthy neonates. Krauss reports that women have better access to the neurologist before pregnancy, less chance of interaction with a neurologist during pregnancy, and an insufficient and often erroneous body of educational advice given to them by obstetricians and neurologists.[22]

In Scotland, surveyed obstetricians reported a lack of neurological resources. Organized collaborative care was available for only 43% of those surveyed. The obstetricians felt their knowledge was inadequate regarding the importance of epilepsy severity, genetic aspects, AED changes and drug levels, use of vitamin K, and breast feeding. Twenty percent expressed dissatisfaction with the care of their epileptic patients. They felt they needed care guidelines.[23] Even in the sophisticated California medical community surrounding Stanford University and with established care parameters, there were gaps in care delivery and knowledge. Only 10% of the pregnancies in women with epilepsy were seen at the university epilepsy center. This clearly bespeaks the need to increase educational efforts aimed at the primary care physician and obstetrician.[24]

The British Epilepsy Foundation surveyed female members.[25] They reported a marked lack of advice on contraception and pregnancy. Although women planning families received the most education, only 80% reported receiving adequate information. Few knew about folate supplementation or possible neural tube defects with AEDs. In London focus groups composed of both epilepsy care nurses and of women with epilepsy reported concerns about continuity of epilepsy care, communication difficulties with medical professionals, shortage of specialists and delays in obtaining appropriate care and treatment.[26]

The fertility rate in women with epilepsy is only 60-80% that of the nonepileptic female population.[13] In the United States, approximately one million women with epilepsy are of child bearing age but produce only 20,000 babies per year. Compared to their siblings, fertility decreases after the onset of epilepsy and worsens with increasing age even when age-matched same sex controls are employed.[27] The explanations proposed for this have been multifactorial: decreased desire, decreased enjoyment, decreased fertility.

Females with epilepsy report normal desire but decreased sexual arousal, suggesting physiological dysfunction. Women with partial seizures reported increased sexual anxiety, dyspareunia, vaginismus, and dissatisfaction. Women with primary generalized epilepsy reported decreased arousal, more anorgasmia, and dissatisfaction. There was no correlation with coexisting depression, sexual experience, AED use, seizure frequency or prepubertal onset. Compared to controls genital blood flow is less increased in women with epilepsy.[28]

Males and females with epilepsy appear to have altered gonadal function. It is unclear whether medications or epilepsy cause this abnormality involving prolactin, luteinizing hormone, estradiol, sex hormone binding globulin (SHBG), dihydroepiandrosterone (DHEAS) in women, and also follicle stimulating hormone (FSH), free testosterone (FT), inhibin, DHEAS and 17α-OH progesterone in men.[29]

Women with epilepsy have been surveyed using established sexuality scales.[30] Desire for intercourse decreased with increasing seizure frequency. There was no difference between women treated with AEDs and those not treated, in desired frequency of intercourse or enjoyment. Treated women tended to be more educated and more "morally strict." Treated women did have higher levels of sex hormone binding globulin and total testosterone. FT, responsible for libido, was not different among the groups.

Marriage rates in individuals with epilepsy and without other neurological deficits are lower--the risk of being single 3.7 times the control. Epileptic patients have a 3.6 fold increased risk of being childless. Patients on AEDs had fewer children and polytherapy patients had a 4 times risk for childlessness. Miscarriage occurred significantly more often (36%) than in untreated (19%) or in control populations (13%). Unlike other studies, this study did not find any difference in congenital abnormalities, psychomotor development or infant epilepsy.[31]

Antiepileptic Drug Effects on Steroid Metabolism

Enzyme inducing anticonvulsant drugs (phenobarbital, phenytoin, carbamazepine, topiramate, oxcarbazepine) are metabolized in the hepatic P450 system (e.g., 3A4, 2C9, 2C19), induce hepatic enzymes, increase the hepatic synthesis of SHBG and increase the metabolism of sex hormones and contraceptive hormones.[29,32] The implications for patients on these AEDs is that low dose ethinyl estradiol (<35 ug) combination pills, progestin-only minipills, and depot estrogen treatment may be potentially ineffective. Breakthrough bleeding does not however, always occur to signal contraceptive failure. In fact contraceptive failure is reported to occur in up to 7% of epilepsy patients on BCPs compared to baseline population risk of 1-2%. Nonenzymic inducing drugs (felbamate, lamotrigine, valproate, gabapentin, vigabatrin) do not interfere with BCPs. (Table 6) Unfortunately this information is not well known by general neurologists and even less well known by obstetricians.[22] Simply increasing the estrogenic component to 50 ug or more prevents contraceptive failure.

DRUG	% FREE	HEPATIC MICROSOMAL METABOLISM	ANTAGONIST VITAMIN K	MALFORMATION		FDA CLASS	OTHER ISSUES
				MAJOR	MINOR		
Phenytoin	5	Induces	+	+	-	D	Coag.
Carbamazepine	25	Induces	+	+	+		Coag.
Phenobarbital	50	Induces	+			D	Coag. Withdrawal Delayed Development
Valproic Acid	50	Inhibitor	-	+	+	D	Neonatal Afibrinogenemia
Ethosuximide	90+	No Effect	+	?	?	C	
Clonazepam	15	No Effect		+	?	C	Tolerance, Sedation, Withdrawal
Lamotrigine	45	± Induces	?	?	?	C	Reduces Folate
Gabapentin	100	No Effect	No Effect	?	?	C	
Felbamate	75	Induces	?	?	?	C	
Topiramate	85	Induces	?	?	?	C	
Tiagabine	4	No Effect	?	?	?	C	
Zonisamide	60	No Effect	?	?	?	NA	
Levetiracetam	90	No Effect	?	?	?	NA	
Vigabatrin	100	No Effect	?	?	?	NA	
Oxcarbazepine	60	No Effect*	?	?	?	NA	

* Reflects nearly complete rapid metabolism to active metabolite that is bound 40%

Table 6. Antiepileptic Drugs in Pregnancy

Congenital Malformations and Other Complications

Ninety percent of pregnancies in women with epilepsy are normal. These pregnancies are generally considered high risk however, because the complications are significantly greater than in the general population.

Seizure frequency may increase during pregnancy in 20-30% of women, more often in patients with partial seizures. Generalized and complex partial seizures have been shown to stress the fetus during obstetrical fetal monitoring studies. This may explain increased fetal loss observed throughout pregnancy and delivery in women with epilepsy.[33]

Teratogenesis is a difficult problem. Until recently most studies have been retrospective, uncontrolled for both seizure frequency and combined polytherapy regimens. More recently the use of monotherapy treatment in women with epilepsy has increased significantly. The educational efforts to utilize folate, to initiate monotherapy prior to pregnancy and to utilize the lowest effective antiepileptic drug doses have decreased the reported incidence of birth defects. Women with epilepsy do have a higher risk of fetal malformations even if they are not treated with AEDs during pregnancy. With AED treatment, the incidence of malformations has been reported as 4-11%, compared to a general population rate of 2-4%. The risk of congenital malformation appears to be greatest with AED polytherapy, VPA levels greater than 70 ug/ml, VPA doses greater than 1000 mg/da, and the combination of

VPA and CBZ.[35] Neural tube defects occur at a higher rate than the population risk for both valproate (2.4%) and carbamazepine (0.8-1.0%). The mechanism/s for the abnormal development are not proven. This may be a attributed to folate deficiency,[35] to increased oxidative metabolic pathways forming arene oxides, or maternal genetic enzyme differences.[36]

All of the common older drugs except carbamazepine are classified by the FDA as Category D drugs, i.e., evidence of risk but benefits may outweigh risk. Carbamazepine and the newer AEDs are all Class C drugs, i.e., adverse effects in animals or studies not available, thus potential risks posed to fetus. (Table 6) Clinical exposure and numbers of deliveries are not yet high enough for any of the new drugs to make statistical statements of safety. Small reports from human studies in phase 3 or 4, some post-approval marketing studies, and registry efforts have not revealed any early major concerns for gabapentin, lamotrigine, topiramate or zonisamide. Case reports have described delivery of normal infants. Unfortunately, the applicability of animal teratogenicity models to human experience in drug development is not verified. There are marked species differences and dosing issues in progression from rodents to humans. Reproductive studies have shown various effects with felbamate, gabapentin, topiramate, tiagabine, and zonisamide.[37,38] Prospective studies and patient registries are important in evaluating AED fetal effects in humans. Whether there are long-term developmental effects on infants has been argued, refuted and argued again. These concerns have centered around learning and neurobehavioral assessments.[39-41]

Male Sexuality

The principal male sex hormone is testicular testosterone. Small amounts of testosterone are produced in the adrenals. Testosterone does have CNS effects. (Table 7) Testosterone levels are greatest during fetal development for masculinization of the urogenital tract in the first few neonatal months, and they then rise again beginning at puberty, continuing over the next three to four decades. Testosterone acts at the Sertoli cells to regulate spermatogenesis and at the seminiferous tubules to regulate semen production. Most of the plasma testosterone is released from the Leydig cells under control of pulsatile hypothalamic regulation and is 98% bound to proteins, albumin and SHBG. (Figure 4) The 2% FT is the active component that acts on target tissues. The 17-OH metabolite (dihydrotestosterone) is the active intracellular agent. Estradiol is the other major active metabolite. Estradiol decreases libido and potency and inhibits LH secretion, resulting in hypogonadotropic hypogonadism. Low FT leads to testicular failure and hypergonadotropic hypogonadism.[42]

Metabolites
Dihydrostestosterone – block glutamate NMDA transmission
Estradiol – potentiate glutamate transmission
Androstenediol – augment GABA chloride transport

Table 7. Testosterone Effects in CNS[13]

Lack of testosterone (hypogonadism) after puberty results in decreased libido, decreased erectile potency, atrophy of the prostate and seminal vesicles and decreased semen production. Replacement of testosterone is limited due to first pass hepatic metabolism.

Effects of Epilepsy and Treatment on Male Sexuality

The Columbia University Fertility Study[27] found male fertility to be decreased after seizure onset, especially if the seizure type was complex partial and there was no family history of seizures. Compared to their male siblings, epileptic men were 36% as likely to father a pregnancy.

Studies on the effects of epilepsy and/or AEDs on male sexuality and fertility are few. Between 50-70% of men with epilepsy report decreased potency and/or libido.[12] In general, FT levels correlate with sexual interest and potency. Estradiol levels correlate with decreased libido and potency and morning erections. Estradiol levels are increased in male epileptic patients.[13] Herzog suggests that the albumin-bound testosterone pool is also readily available to the tissues as is FT. An index accounting for FT and the "non-SHBG-bound testosterone" more accurately may describe the physiologic state.[43] Not accounting for this additional pool may explain the disparity in conflicting reports.

In a small series of eight hyposexual males, only three had FT levels below normal range, although the normal group had twice the levels of the hyposexual group.[13] This disparity may

be due to the additional "available" (albumin bound or "non-SHBG bound") testosterone pool. Treatment of hyposexual males with testosterone has not consistently improved function. If testolactone, an inhibitor of the aromatase that converts testosterone to estradiol, is utilized, there is a significant improvement in function and decrease in seizure frequency correlating with the decrease in estradiol levels, not the testosterone levels. Depo-testosterone 400 mg/IM. bi-weekly is administered with 3-500 mg/day testolactone, which is titrated to bring the estradiol to 20-40 pg/ml.[13] Testosterone esters are most effective in intramuscular preparations, being hydrolyzed to testosterone in vitro.

In 31% of male epileptic patients FSH is increased. This indicates impaired spermatogenesis and sperm motility. Fifty percent have a decreased testosterone:LH ratio, implying impaired Leydig cell function. Although LH is increased significantly these impaired Leydig cells are unable to increase testosterone synthesis. Adrenal androgens, DHEAS and 17∝-hydroxyprogesterone are also lower. Total testosterone levels are normal. Hepatic SHBG synthesis is significantly increased due to therapy with inducing AEDs. Inhibin is a polypeptide secreted by testicular Sertoli cells. It suppresses FSH secretion, correlates inversely with sperm count and serves as an indicator of spermatogenesis. It is decreased in 12% of males with epilepsy, thus testicular function is impaired.[2,28,42]

Males with epilepsy who are treated with enzyme inducing agents have decreased FT, elevated LH and increased SHBG. Pituitary responsiveness is the same as that of controls. Valproate does not produce this effect.[44] Untreated epileptic males have the same hormonal

profile as normal controls. A study by Isojarvi of sixty-three treated epileptic males demonstrated AED effects on the hypothalamic-pituitary axis and found VPA monotherapy to be the least disruptive to male hormone levels.[45]

A group of 37 adult males without a previously known sexual history, who were seizure free for five years on monotherapy (12 with idiopathic generalized epilepsy, 25 partial epilepsies) and who had normal EEGs were consecutively entered into study. Sexuality was assessed by interview and was normal in 75% of the men with generalized seizures and 25% of the men with partial seizures. Hyposexual men had higher estradiol levels. Impotent males had low free testosterone:estradiol and dihydrotestosterone:estradiol ratios. LH peaks after LHRH-TRH infusion were significantly lower in hyposexual males than normal controls, suggesting they suffered subclinical hypogonadotropic hypogonadism. [46]

One hundred-eighteen epileptic men on AEDs, 32 not on AEDs, and 34 controls were compared. SHBG levels were significantly elevated in the treated group but neither patient group differed from controls in FT, estradiol or androstenedione nor in sexual function as assessed by standardized sexuality questionaires.[47]

Evaluation of animal and human frontal and limbic circuits reveal CNS neurogenic erectile control. Nine males were studied with nocturnal tumescence and rigidity studies: eight with uncontrolled temporal lobe epilepsy (TLE) and one with nonepileptic events. All were on antiepileptic drugs and seven reported erectile dysfunction. None were institutionalized, had

psychiatric illness or consumed other medications that could affect penile function. Abnormal studies were seen in five patients with TLE who also reported dysfunction. These individuals had decreased rigidity suggesting neurogenic dysfunction. None of the subjects had abnormally low sexual desire.[48]

It is not clear what is the main etiologic factor in male sexuality and/or fertility problems. The evaluation must, therefore, be multifactorial. The history must be accurately and thoroughly obtained. Medications effects, depression, psychosocial contributions and physiologic dysfunction must all be evaluated. The "cure" or "fix" may not be easily discerned. Reversible factors must be corrected, the contribution of other medical diseases and medications must be assessed. Serum levels of FT, non-SHBG binding protein, estradiol, LH and FSH should be obtained. Urological consultation should be obtained to determine if vasogenic or neurologic penile dysfunction is present and what therapies may be appropriate for the individual (testosterone replacement, change of AED to a non-enzyme inducing agent, sildenafil (Viagra) treatment or device implant).

Summary:

Male and female sexuality and reproductive functions are complex systems with cortical, limbic system, hypothalamic, pituitary and sexual end organ interactions. Progesterone, estrogen and testosterone have neuroendocrine effects that alter epileptogenicity. Seizure frequency may change throughout the life cycle as a result of hormonal status. Antiepileptic drugs interact with hormone binding metabolism resulting in altered human reproductive

function. AEDs alter contraceptive hormone treatments. Catamenial epilepsy and some sexual dysfunction in males may be treatable.

Conclusion:

There does not seem to be definitive solutions for either men or women with epilepsy regarding problems with sexuality or fertility. Education, effective and simplified care of the epileptic patient, psychosocial interventions and hormonal treatments may all be necessary in those individuals who have difficulties. Women with epilepsy have the additional concern regarding contraception, pregnancy and successful childbearing. All of these issues must be knowledgeably addressed by the treating neurologist, obstetrician-gynecologist and primary physician.

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