INTRODUCTION

To the Physician:

Use this background material and checklist as a guide for discussions of important issues with teens & women of all ages who have epilepsy. This is not a script, but a reminder of major topics as well as documentation of your discussion with the patient. Please use the accompanying Discussion Guide for specific information.

The checklist is divided into sections appropriate to different life stages.

Patients with new-onset epilepsy, and those new to your practice, require detailed information; continuing patients may need follow-up discussions as they mature & their situations change. The status of teens & women who are not currently sexually active could change between visits. They may need up-to-date information & options appropriate to their current lifestyle. Women approaching menopause have their own specific concerns.

Check all areas covered in this visit, date and sign this form, & have your patient sign it as well. File the form in the patient's chart for reference at subsequent visits. Download background information for your use & patient handout materials from http://www.professionals.epilepsy.com. Make notes of specific strategies discussed for follow-up discussions and refer patients to http://www.epilepsy.com for information.

Co-Editors
Steven Schachter MD
Orrin Devinsky MD
Joyce Cramer BS

Reviewers
Elinor Ben Menachem MD
Jane Boggs MD
Edward Bromfield MD
Carol Camfield MD
Jacqueline French MD
Sandra Helmers MD
Andres Kanner MD
Kevin Kelly MD
Gregory Krauss MD
Joyce Liporace MD
Richard Mattson MD
Kimford Meador MD
Georgia Montouris MD
William Rosenfeld MD
Patricia Osborne Shafer MSN
William Tatum MD
Braxton Wannamaker MD
James Wheless MD
Mark Yerby MD
# TABLE OF CONTENTS

## INTRODUCTION

### TABLE OF CONTENTS

### FOR ALL WOMEN, ADOLESCENTS, AND PRE-TEENS DURING REPRODUCTIVE YEARS

- **Relationship Between Hormones and Epilepsy (Overview)** ........................................... 4
  - Selected References ........................................................................................................... 6
- **Epilepsy and the Menstrual Cycle: Catamenial Epilepsy** ................................................... 7
  - Management ....................................................................................................................... 8
  - Selected References ........................................................................................................... 9
- **Impact of Epilepsy on Sexual and on Reproductive Issues** ........................................... 10
- **Sexual Dysfunction** ........................................................................................................ 11
  - Selected References ........................................................................................................... 14
- **Impact of Careful Pregnancy Planning** ........................................................................ 15
  - Non-OC Forms of Contraception ...................................................................................... 17
  - Selected References ........................................................................................................... 18

## Women Planning to Conceive

- **Healthy Pregnancies and Healthy Babies** .................................................................... 20
  - Pregnancy Risks ............................................................................................................... 20
  - Fetal and Post-partum Risks Associated with Epilepsy ................................................... 21
  - Need for Folate Supplementation (especially if patient is taking any enzyme-inducing drug) .......................................................... 21
  - Selected References ........................................................................................................... 23
  - AEDs During Pregnancy .................................................................................................. 23
  - Teratogenesis .................................................................................................................... 24
  - Prenatal Screening ........................................................................................................... 26
  - Labor and Delivery ........................................................................................................... 26
  - Vitamin K Recommendations ......................................................................................... 27
  - Postpartum Care and Breastfeeding .............................................................................. 27
  - Parenting Issues and Safety ............................................................................................ 28
  - Selected References ........................................................................................................... 28

## Women Beyond Childbearing Years

- **Importance of Folate Supplementation** ...................................................................... 30
MENOPAUSE, DEFINITIONS ...............................................................................................................................30
PERIMENOPAUSE AND EPILEPSY .....................................................................................................................31
EARLY MENOPAUSE WITH EPILEPSY ...............................................................................................................31
HORMONE REPLACEMENT THERAPY ...............................................................................................................32
BONE HEALTH ................................................................................................................................................32
AGE AND AEDs ..............................................................................................................................................34
SELECTED REFERENCES .................................................................................................................................34

REFERENCES ..................................................................................................................................................35

PHYSICIAN’S DISCUSSION CHECKLIST FOR WOMEN WITH EPILEPSY ...........42

FOR ALL WOMEN, ADOLESCENTS, & PRE-TEENS DURING REPRODUCTIVE YEARS ....42
WOMEN PLANNING TO CONCEIVE ...............................................................................................................43
PREGNANT WOMEN .......................................................................................................................................44
WOMEN BEYOND CHILDBEARING YEARS ....................................................................................................44
FOR ALL WOMEN, ADOLESCENTS, AND PRE-TEENS DURING REPRODUCTIVE YEARS

Relationship Between Hormones and Epilepsy (Overview)

Women with epilepsy have particular challenges that are related to ovarian steroid hormones. The ways in which hormones affect their seizure activity begins to be evident at the start of menstruation. Women may have changes in seizure threshold related to their menstrual cycle as well as at other times in their reproductive life including puberty, pregnancy, and menopause, all times when there are changes in the estrogen and progesterone levels in the body. Fertility and reproductive capacity may be affected in some women with epilepsy. In many ways, hormones influence epilepsy and epilepsy influences hormones. Estrogen can be a very potent proconvulsant, while progesterone can be anticonvulsant. Research into this complex interaction is ongoing, but much is known that can help physicians as they manage female patients through all of the phases of their reproductive life while maintaining optimal control of their epilepsy.

Ovarian sex-steroid hormones affect the excitability of the central nervous system (CNS) and alter the frequency and severity of seizures. The principal ovarian steroid hormones are estrogens (estradiol, estrone, and estriol) and progesterone, with their secretion controlled by the hypothalamus and pituitary. Estradiol is the most potent estrogen. A complex neuroendocrinologic feedback system, the hypothalamic-pituitary-ovarian axis [see figure], regulates the menstrual cycle. Gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) by the pituitary. FSH stimulates formation of the ovarian follicles, which secrete estradiol as they develop. FSH is inhibited while GnRH is stimulated by estrogen. One result is a surge of luteinizing hormone (LH), which induces oocyte maturation, ovulation, and conversion of the follicle into the corpus luteum. This marks the end of the follicular phase of the cycle preceding ovulation by about 36 hours. Following ovulation, the luteal phase commences when the corpus luteum secretes progesterone. The progesterone inhibits secretion of GnRH, FSH, and LH. If there is no pregnancy, the corpus luteum regresses and production of progesterone and estradiol decline. When the progesterone secretion tapers off and GnRH inhibition decreases, the cycle repeats in a loop.
Estradiol and progesterone are highly lipophilic and easily cross the blood-brain barrier and diffuse through cell membranes, binding to intracellular receptors and forming a hormone-receptor complex. The fluctuations in ovarian steroids and peptides directly affect the brain. Hormones from the hypothalamus and pituitary gland regulate the amount of estrogen and progesterone circulating in a woman’s body. The hypothalamus, in turn, receives many direct connections from those parts of the temporal lobe that are involved in the generation of seizures. Alteration of normal LH pulsatile secretion has been documented in women with epilepsy. Chronic epilepsy and the seizure event itself have different effects on LH pulsatility. Research has shown that seizure discharges can disrupt the output of hormones such as FSH and LH, which in turn can alter the balance of estrogen and progesterone and affect seizure control. In other words, seizures can affect hormones, and hormone levels can also affect seizures.

Experimental models of epilepsy demonstrate a change in seizure susceptibility provoked by the ovarian steroid hormones. These hormones alter the excitability of neurons in the brain, particularly in the temporal and frontal lobes.

Animal models have demonstrated proconvulsant effects of estrogen and anti-convulsant effects of progesterone. Estrogen increases excitatory neurotransmitters and also alters
dopamine, which is an inhibitory neurotransmitter. Estrogen may also alter the structure of the synaptic area of neurons, increasing the number of dendritic spines and the number of spine synapses, thereby increasing cell-to-cell contacts.

Since the antiseizure effect of progesterone is present in progesterone-receptor knockout mice, it can be assumed that progesterone exerts its seizure-inhibitory effects through its metabolites. Those metabolites are sometimes referred to as neuroactive steroids. Allopregnanolone is a GABAA-receptor–modulating neurosteroid progesterone metabolite. Metabolites of progesterone regulate hippocampal neuronal excitability, with a positive allosteric effect on GABA-A receptors. In animal models of epilepsy, progesterone raises the seizure threshold. Progesterone metabolites produce anticonvulsant, antianxiety, and sedative effects similar to those of benzodiazepines. For this reason, researchers are working on developing progesterone-based antiepileptic medications that may have fewer adverse effects than current AEDs.

The effects of estrogen and progesterone demonstrated in experimental models of epilepsy have also been seen clinically. Women with epilepsy have exhibited a variety of endocrine disturbances. These have been attributed to a combination of factors, including the epilepsy syndrome and the effect of interictal and ictal epileptic discharges in the brain. The risk is exacerbated by the effects of some antiepileptic drugs (AEDs). The relation between a particular AED and the endocrine system appears to result from the drug’s effect on hepatic microsomal enzymes of the cytochrome P-450 system. For example, AEDs that induce hepatic microsomal enzymes (EIAEDs) also interact with hormonal contraception to increase estrogen’s metabolism and progesterone's protein binding, thereby decreasing concentrations for both hormones and thus reducing contraceptive efficacy.

Normally, estrogen levels are higher than progesterone levels in the days leading up to ovulation and immediately before menstrual bleeding. These are the times in the menstrual cycle during which many women notice more frequent and/or more severe seizures (especially just before menstruation). If a woman has menstrual cycles in which she does not ovulate, she may not have enough progesterone during the entire second half of the menstrual cycle. In this circumstance, during anovulatory cycles, seizures may be worse for the entire second half of the cycle. These relationships are explored in the next section this guide.

**Selected References**

Epilepsy and the Menstrual Cycle: Catamenial Epilepsy

Seizures often occur in clusters. For women, that increase in seizure frequency may be related to the menstrual cycle. Catamenial epilepsy is a term used to describe patterns of seizures that occur in association with the menstrual cycle, especially around menstruation, and is believed to be related to the neuroactive properties of estradiol and progesterone and to the cyclical variation in their serum levels. Catamenial epilepsy affects between 40% and 70% of women with epilepsy, depending on the definition used. More than 70% of women with epilepsy may have an exacerbation of seizures in relation to menses; however approximately 35% have a significant, two-fold or greater increase in seizure frequency. It is difficult to know the precise number of women with catamenial epilepsy partly because women may either under- or over-report this phenomenon and partly because the definition has not been consistent across studies. A uniform definition of this phenomenon should be a help to physicians in recognizing, consistently diagnosing, and managing the disorder. The many researchers who have seen a pattern of seizure exacerbation associated with the menstrual cycle have defined catamenial epilepsy broadly, as seizure frequency greater than normal during a specific phase of the menstrual cycle rather than more narrowly determining specific patterns of seizure cluster.
When first described, catamenial seizures were said to occur only immediately before or during the onset of menstruation. More recently, three patterns of catamenial seizures have been described as perimenstrual (estrogen and progesterone levels are low), periovulatory (estrogen levels are high, progesterone levels are low), and inadequate luteal phase (inadequate progesterone) catamenial epilepsy. For women with normal menstrual cycles, the perimenstrual and periovulatory patterns are seen most often: seizures occurring before or during the first few days of menstruation (day -3 to day 3, where day 0 is the first day of menstrual bleeding) and seizures at the time of ovulation (days 10-13). The third pattern of seizure exacerbation is seen in women with abnormal menstrual cycles who do not ovulate regularly. The pattern of inadequate luteal phase exacerbation of seizures occurs during the entire second half of the menstrual cycle.

The mechanisms that underlie development of a catamenial epilepsy seizure pattern are not yet well understood. Recent studies suggest that cyclical changes of ovarian hormones estrogens (proconvulsant) and progesterone (anticonvulsant) appear to play a key role. Estrogen-mediated increases in brain-derived neurotrophic factor (BDNF) synthesis may lead to excess glutamate release that contributes to increased hippocampal excitability. When estrogen levels are high relative to progesterone, as occurs just preceding and in the first few days of menses, the likelihood of seizures would increase. Elevations of the estrogen level during ovulation and low levels of progesterone during the luteal phase of anovulatory cycles are among the factors that precipitate catamenial epilepsy. Progesterone metabolites reduce seizure susceptibility partly through conversion of progesterone to neurosteroids such as allopregnanolone, which enhances GABA (A) receptor function and thereby inhibits neuronal excitability. Neurosteroids have been shown to be very effective inhibitors of catamenial seizures in animal models.

Variations in concentrations of antiepileptic drugs across the menstrual cycle may also contribute to increased seizure susceptibility. Estrogen and progesterone are metabolized by the same liver enzymes that metabolize most of the commonly used enzyme-inducing seizure medications. As estrogen and progesterone levels change throughout the menstrual cycle, there may be an effect on the way AEDs are metabolized by the liver enzymes. A resulting decrease of AED serum levels on the days that precede menstruation can also contribute to premenstrual seizure exacerbation. It is supposed that the lower serum level of antiepileptic drugs is due to an increase in their metabolism by the hepatic microsomal enzyme system that is mediated by gonadal steroids.

**Management**

Management of catamenial epilepsy first requires determining whether the seizure pattern in fact fits a definition of catamenial epilepsy. For accurate diagnosis, a patient must keep a careful seizure diary with notation of menstrual cycle dates and seizure occurrence and type for a minimum of 3 monthly cycles in order to determine if a pattern exists. Women who know when they ovulate should record that information as well. They may detect
ovulation from mid-cycle vaginal discharges, mid-cycle mild cramping, or by a change in basal body temperature. For some women, a blood test on day 22 of the menstrual cycle can measure circulating progesterone level. The seizure diary should include information about factors that may affect seizures such as missed medication, stress, and lack of sleep. In addition, testing for changes of AED levels during the menstrual cycle can be helpful.

Current approaches to the treatment of catamenial epilepsy are based on small, non-blinded studies and/or on anecdotal reports of success. No FDA-approved drug has an indication specifically for catamenial epilepsy. Some treatments explored for women experiencing catamenial epilepsy have utilized hormonal manipulation to address the relation between ovarian hormones and seizure exacerbation. A large, randomized, placebo-controlled study of the effects of a progesterone supplement on catamential epilepsy is underway. Preliminary results from an open series were favorable. There have been extreme measures such as hysterectomy or oophorectomy and more conservative attempts involving oral contraceptives, natural progesterone, and the estrogen-receptor antagonist clomiphene. Other therapies have included perimenstrual increases in AED doses, treatment with acetazolamide, and premenstrual introduction of short-term treatments, usually benzodiazepines. Open trials have shown that some women with epilepsy have had success with natural high-dose progesterone therapy. Synthetic neurosteroids without hormonal side effects are being evaluated for catamenial epilepsy. Ganaxolone, an orally active GABA (A) receptor-modulating synthetic neuroactive steroid, is one promising investigational treatment for catamenial epilepsy. Another is the development of a BDNF antagonist for use during the periovulatory period. A comprehensive treatment for catamenial epilepsy may need to address both the estrogen and progesterone contributions to catamenial epilepsy. Since the different patterns may respond differentially to therapeutic intervention, treatment choices are likely to be complex.

Thus far, in spite of an increased variety of both antiepileptic and hormonal drugs, catamenial seizures may remain refractory to many treatments in some women. Thus, neurologists usually work with primary care clinicians, obstetricians/gynecologists, and endocrinologists or neuroendocrinologists to develop a treatment strategy. Ongoing research leading to a deeper understanding of the causes of catamenial epilepsy is likely to provide better therapeutic options requiring periodic reevaluations of affected patients.

Selected References

- Crawford P, Lee P. Gender difference in management of epilepsy—what women are hearing. Seizure 1999;8:135-139.
Impact of Epilepsy on Sexual and on Reproductive Issues

Epilepsy has an influence on many aspects of sexual and reproductive functioning. The majority of women with epilepsy (WWE) are able to have normal sexual lives, to become pregnant, and to deliver normal babies. Nevertheless, a large number of WWE have some degree of sexual and/or reproductive dysfunction. Sexual dysfunction may include difficulty with libido, arousal, and orgasm. Fluctuating hormone levels may contribute to difficulties in menstruation. One-third to one-half of women with temporal lobe epilepsy report difficulties with their menstrual cycle, with 20% having amenorrhea (absence of menstruation). In addition to amenorrhea, they may experience oligomenorrhea (extended menstrual cycles), or unusually long or short times between menstrual periods. Some women experience anovulatory cycles, in which ovulation doesn’t occur, a corpus luteum is not formed, and there is an inadequate luteal menstrual phase. In such cases
progesterone is not secreted. Women with menstrual cycles shorter than 21 days or longer than 35 days, those with breakthrough bleeding and those with bleeding that lasts for more than 7 days should be referred to an endocrinologist or a gynecologist for evaluation.

The association between epilepsy and reproductive endocrine disorders is a matter of controversy. Epilepsy is associated with these disorders by itself. But AED therapy may have a greater effect on endocrine function. As always, all of the benefits of a therapy must be weighed against the potential risks.

**Sexual Dysfunction**

Epilepsy is associated with a higher incidence of sexual dysfunction when compared with other neurologic disorders. Sexual dysfunction has been reported in 14% - 50% of women and 30% - 66% of men with epilepsy. Between 25% and 34% of women with epilepsy report diminished sexual desire. Libido difficulties are reported more in individuals with complex partial than generalized seizures. One survey of sexual desire found a proportional decrease in desire for intercourse with increasing seizure frequency. Psychosocial and developmental impairment may be responsible for sexual dysfunction in some WWE; however, there are specific physiological causes as well. In terms of the psychosocial factors, clinical depression and anxiety regarding seizures during sexual activity are two of the possible contributors to sexual dysfunction; however, some studies have found no correlation between sexual dysfunction and coexisting depression, sexual experience, AED use, seizure frequency, or pre-pubertal onset of epilepsy.

Physiologically, the areas of the brain that mediate sexual behavior are the same areas that are involved in common forms of focal epilepsy. Some women report normal sexual desire but difficult or painful coitus (dyspareunia), lack or vaginal lubrication, and/or vaginismus even when there is sexual desire and arousal. Some studies have found lack of adequate increases in genital blood flow even when a woman experiences subjective arousal. This diminished vaginal blood flow affects sexual functioning.

Some antiepileptic drugs may adversely affect sexual function, particularly antidepressants and drugs that increase serotonin levels. Barbiturates are known to reduce libido/potency. There have been a small number of cases of anorgasmia reported in women taking gabapentin, which appear to be dose related. A decrease in dose or a change in dose regimen to maximize the time interval between drug ingestion and sexual activity may be sufficient to minimize this effect. Some studies have found that transdermal testosterone replacement (not currently approved by the FDA for treatment of women) may improve sexual function. Resective brain surgery as a treatment for medically refractory seizures has also been shown to restore sexual function. For some women, non-prescription vaginal lubricants may be helpful. Sildenafil (Viagra®) is also being studied to improve the vasocongestion in women. Counseling may be beneficial for
some women. Finally, careful consideration of AED therapy and a possible change in AED may be considered.

A patient’s report of sexual dysfunction should merit a careful evaluation of psychosocial factors as well as physiological factors. A careful history, physical examination, and a series of laboratory measurements may be indicated.

**Infertility; Polycystic Ovarian Syndrome (PCOS)**

Most women with epilepsy are able to conceive. However, as would be expected, altered menstrual cycles and other factors can result in reduced fertility. In studies, women with epilepsy have a fertility rate 60% - 80% of that of women without epilepsy. AEDs may contribute to infertility in some women, with polytherapy having a greater detrimental effect than monotherapy. Fertility has been found to decrease after the onset of epilepsy in some women and to worsen with increasing age at a greater rate than in controls. As is the case with general sexual dysfunction, most of the mechanisms related to infertility, defined as failure to conceive after 1 year of regular unprotected intercourse, are physiological and hormonal based. Nevertheless, clinical depression reported in some women with epilepsy may also be associated with infertility. Women with epilepsy are at risk for polycystic ovaries, a major contributor to infertility. Other contributors to reduced fertility may be: hypogonadotropic hypogonadism (reduced gonadal stimulating pituitary hormones FSH [follicle stimulating hormone] and LH [luteinizing hormone]) and hypergonadotropic hypogonadism (insufficient amounts of sex hormones to suppress LH and FSH to normal levels through the usual negative feedback mechanism), oligomenorrhea and amenorrhea. Anovulatory cycles may be yet another cause of infertility. Women with epilepsy are eligible for fertility treatment whether or not they are taking anti-epileptic drugs (AEDs). However, a small number of women may experience an increase in the number of seizures when taking certain hormone-based fertility drugs.

Polycystic ovarian syndrome (PCOS), a reproductive endocrine disorder, is one of the leading causes of infertility in women and is estimated to affect 4% -6% of all women of childbearing age. Isolated polycystic ovaries are found in 17% - 33% of the general population of women, but should not be confused with PCOS. Only some women with polycystic ovaries develop PCOS, characterized by chronic oligomenorrhea (menstrual cycle >35 days) or amenorrhea (no menses >6 months) associated with increased serum androgen levels.

In women with PCOS, the ovaries have multiple cysts and there are other components of the syndrome including obesity, high cholesterol and lipid levels, acne and hirsutism, elevated LH/FSH ratio, chronic anovulation, and elevated serum androgen levels. Not all of these components need to be present. Nevertheless, women presenting with these symptoms should be investigated for possible PCOS, regardless of AED regimen. The
features required for the diagnosis are polycystic ovaries, hyperandrogenism, and frequent anovulatory cycles. PCOS occurs more frequently in women with temporal lobe epilepsy (10% - 25%) than in the general population (4% - 6%). The syndrome is a form of hyperandrogenic chronic anovulation, which may have insulin resistance as its basis.

Some studies suggest that valproate (VPA) is associated with PCOS, particularly in obese women. Up to 60% of women with epilepsy treated with VPA have ovaries with polycystic appearance, compared with 25% - 30% of women in the general population. This prevalence is highest in women who began VPA therapy before the age of 26. VPA-associated weight gain and polycystic ovaries were found to be common in women with epilepsy who began treatment prior to age 20. One recent large, multiethnic, randomized study found that a greater proportion of women taking VPA than those taking lamotrigine developed components of PCOS. Some studies have demonstrated that this condition is reversible if therapy is changed to another AED, perhaps because the VPA inhibition of steroid hormone metabolism is eliminated and enzyme induction by the new AED, if it is an EIAED, increases steroid hormone metabolism. Another study found that women taking VPA had significantly higher testosterone and free-androgen than those taking LTG; however, testosterone levels were outside the normal range in only two women. And menstrual cycle abnormalities were found in a greater percentage of women taking VPA monotherapy than those taking LTG monotherapy. A larger study of women given either LTG or VPA monotherapy for less than 5 years found that while insulin levels in the two groups did not differ significantly, the VPA-treated patients gained more weight. Nevertheless, in this study the two groups showed no significant difference in menstrual cycle regularity or in anovulation, though the mean serum testosterone levels were higher in the VPA group.

Caution is needed when reviewing these data, since most studies have had small numbers of patients and inadequate study design. A 15-month study of nonepileptic normal cycling monkeys exposed to therapeutic doses of VPA found no cyclic hormonal or morphological ovarian abnormalities or characteristics of the PCOS. EIAEDs induce cytochrome P-450, accelerate hepatic biotransformation, and increase binding and metabolism of testosterone, thereby reducing testosterone serum levels. These AEDs may affect the hyperandrogenism, reducing the occurrence of polycystic ovaries. Such an effect may account for a discrepancy between VPA and EIAEDs in studies of PSOS. In addition, it is important to recognize that VPA is widely used to treat primary generalized epilepsies with onset in childhood and adolescence. This contributes to the larger number of female patients treated from young age, during their sexual development. The reproductive endocrine effects of the newer AEDs are current being studied.

Hypothalamic or hypogonadotropic amenorrhea occurs in about 12% of women with temporal lobe epilepsy, as compared to 1.5% of the general population. In this condition there is low pituitary FSH and LH production as well as low estrogen levels. This condition as well as PCOS is associated with inadequate luteal phase cycles, which can
result in infertility and increased seizure occurrence. Left unilateral temporo-limbic epilepsy has been associated with PCOS; right temporo-limbic epilepsy has been associated with hypothalamic amenorrhea.

Women experiencing difficulties with fertility may need assessment with endocrine testing, pelvic ultrasound, and pituitary imaging. The possible benefits of a change in AED therapy must be balanced against seizure efficacy and the adverse event profile of the current and alternative AED.

**Selected References**


### Importance of Careful Pregnancy Planning

The majority of women with epilepsy CAN become pregnant, whether or not they are taking AEDs. The possibility of becoming pregnant should be considered for any woman with epilepsy who is of childbearing age. It has been estimated that as many as 40% of women with epilepsy have unplanned pregnancies. This is of particular importance because of the maternal and fetal risks associated with pregnancy for some women with epilepsy. Beginning in adolescence, it is important to be sure that all female patients have full information regarding effective contraception. Contraceptive management requires careful consideration and is closely tied to epilepsy management.

There are a number of safe and effective methods of contraception available. Like all women, women with epilepsy must carefully consider their best contraceptive option; however, they need additional information regarding the possible interaction of their epilepsy medication and contraceptive choice. Most hormonal oral contraceptives (OCs) combine synthetic estrogen and progesterone. Both hormones affect seizure activity, with
estrogen generally proconvulsant and progesterone generally anticonvulsant. While most current guidelines suggest that the combination oral contraceptive (COC) pills give a sufficient dose of estrogen to inhibit ovulation, generally > 35 μg, it is the progestin component that induces contraception and the estrogen component that prevents breakthrough bleeding is only indirectly involved in contraceptive efficacy.

Some first and second generation AEDs induce hepatic cytochrome P450 (CYP 450) enzyme activity and increase the metabolism of both estrogen and progesterone. This decreases the concentration of biologically active hormone and can make the combined OC ineffective leaving the woman at risk for an unplanned pregnancy. Even small increases in metabolism may lead to contraceptive failure. Women taking hepatic microsomal enzyme-inducing AEDs (EIAEDs) may have as much as a five-to-sixfold increase in the COC failure rate.

Most drugs that inhibit or have no effect on the CYP450 enzyme system do not affect the efficacy of hormonal contraception. Lamotrigine is the exception; though it is not an EIAED, it is reported to interact with COCs and may reduce contraceptive effectiveness. One study found a modest decrease in the plasma concentration of levonorgestrel although there was no corresponding hormonal evidence of ovulation. Another recent study suggested a decrease in norethisterone concentrations in patients receiving lamotrigine, which could put a woman at increased risk for an unplanned pregnancy.

Fully effective contraception cannot be guaranteed with either lamotrigine or topiramate (>200 mg/day), though ovulation does not appear to occur with these drugs. In addition, lamotrigine trough levels are decreased 25% - 70% with COC administration and returned to 80% - 100% of baseline during the pill-free week. Therefore, women taking lamotrigine and a COC need careful monitoring and selection of optimal formulation of COC. Research is ongoing regarding the newer AEDs.

The table below lists AEDs according to their reported interactions with COCs [see table].

Women taking combined OCs with a low dosage of hormones are at particular risk. To minimize the risk of hormone-related side effects, standard prescribed oral contraceptives contain only the minimal dosage of hormone required to inhibit ovulation. For women with epilepsy taking EIAEDs, COCs containing 1 mg of norethidrone, 0.150 mg of levonorgestrel, or 0.300 mg norgestral are recommended. Combined OCs with at least 50 μg of the estrogen component are recommended. If there is breakthrough bleeding, the estrogen dose may be increased to 75 – 100 μg daily. The risk of adverse effects related to estrogen at these high dosages is limited because the combined OC reduces the circulating plasma estrogen level to normal low-dose levels. If breakthrough bleeding occurs when taking an OC, the hormonal dosage should be increased for the remainder of the cycle to increase the likelihood of effective birth control.
Hormonal contraception remains a reasonable option for women with epilepsy with some exceptions. One suggestion for patients taking AEDs that interfere with COCs is to use a barrier method of contraception, such as condoms, the diaphragm, or the cervical cap, in addition to the COC. Another is to consider epilepsy management using an AED that has no interaction with COCs.

<table>
<thead>
<tr>
<th>Non-EIAED – no reported interaction with OCs</th>
<th>EIAED – interacts with OCs</th>
<th>Non EIAED – interacts with OCs</th>
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<tbody>
<tr>
<td>Clobazam</td>
<td>Barbituates</td>
<td>Lamotrigine</td>
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<tr>
<td>Clonazepam</td>
<td>Carbamazepine</td>
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<td>Felbamate</td>
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<td>Gabapentin</td>
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<td>Primidone</td>
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<td>Levetiracetam</td>
<td>Topiramate (&gt;200 mg/day)</td>
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<td>Pregabalin</td>
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<td>Tiagabine</td>
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<td>Valproate</td>
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<td>Zonisamide</td>
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Though the data are sparse at this time, it is assumed that progesterone-only OCs are also affected by EIAEDs, making this method of contraception not recommended for women with epilepsy.

**Non-OC Forms of Contraception**

EIAEDs reduce the contraceptive efficacy of levonogestrel implants (Norplant). Intramuscular medroxyprogesterone (Depo-Provera) removes the compliance issues that are a particular problem for adolescents and women with cognitive impairment, and may be used since it has not been seen to be affected by AEDs. It is recommended that injections be administered every 10 weeks (and some clinicians prefer every 6 – 8 weeks) rather than the usual 12 weeks for women with epilepsy. A new low-dose formulation (Depo-SubQ Provera 10) is not recommended for women taking EIAEDs due to the possibility of decreased efficacy caused by increased rates of steroid metabolism. Long-term use of medroxyprogesterone may decrease bone mineral density, so this is not a long-term solution. If post-coital contraception is used after unprotected sexual activity, the “morning after pill” containing levonorgestrel, some practitioners recommend that the first dose should be doubled to two pills (1.5 mg). A second dose of one pill is then taken 12 hours later. More research is needed in this area.
Intrauterine devices that secrete progestin (IUD), also known as the coil, may be used. The Mirena coil, approved by the FDA in 2000, secretes 20 μg/day levonorgestrel hormone locally in the uterus and remains active for 5 years. This contraceptive method may be used by women with epilepsy and does not appear to be affected by EIAEDs. A copper IUD, Paraguard, is also effective for WWE taking EIAEDs.

Both the rhythm method and Persona rely on hormonal changes to determine “safe” times for sexual activity. Persona is a relatively new contraceptive method that relies on using a special monitoring system for testing urine for hormonal changes that affect ovulation. The manufacturer suggests that Persona is “ideally suited for women in stable relationships who intend to have children in the future and who have regular cycles between 23 and 35 days in length,” and is 94% effective if used properly. However, this method is contraindicated for women with epilepsy who take EIAEDs since the hormone levels in urine may be affected by both epilepsy itself and by AEDs. The rhythm method presents a similar problem and is not a reliable method of birth control for women with epilepsy.

Transdermal contraception is delivered via a patch. Ortho Evra, the first in this category approved by the FDA, is a combination of norelgestromin and ethinylestradiol. A new patch is applied weekly for 3 weeks. Menstruation occurs during the 4th week with no patch. While the studies have not yet been done, it is possible that EIAEDs may reduce the effectiveness of the patch because of the low-progestin dose and increased metabolism of the steroid components. This method is, therefore, not recommended for women taking EIAEDs.

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WOMEN PLANNING TO CONCEIVE

PREGNANT WOMEN

Healthy Pregnancies and Healthy Babies

After migraine, epilepsy is the neurologic condition most often seen in pregnant women. Approximately 0.3% to 0.5% of all births are with mothers who have a seizure disorder. For women with epilepsy (WWE), healthy pregnancies & healthy babies are the goal while maintaining optimum seizure control. Over time there have been numerous reports of both the effects of pregnancy on seizure activity and the teratogenic effects associated with antiepileptic drugs (AEDs); however, the vast majority of pregnancies (>90%) in women with epilepsy result in healthy babies. Nevertheless, WWE have a two-to-three fold increase in the chance of having a baby with a major malformation than nonepileptic women. As more and more women with epilepsy have received good prenatal care, careful monitoring during pregnancy, and folate supplementation, both maternal and fetal health statistics have improved with respect to complications. This makes optimal care essential for WWE of childbearing age. Still, worldwide, women have reported that they receive inadequate or conflicting information regarding their epilepsy and pregnancy.

Pregnancy Risks

All pregnant women face some risks. For women with epilepsy, good seizure control is of paramount importance. One-quarter to one-third of WWE have an increase in seizure frequency during pregnancy. This appears to be unrelated to seizure type, duration of epilepsy, or seizure experience in any prior pregnancy. The increase may be due to sleep deprivation or difficulty in maintaining steady AED blood levels during pregnancy. Those women who have an increase in their seizure frequency may have reduced AED blood levels compared to pre-pregnancy. Careful monitoring of AED levels is needed throughout pregnancy and dose adjustment may be required to keep blood levels in the appropriate range. Careful attention should also be paid to compliance with the AED regimen since some WWE may reduce their medication because they are afraid of potential damage to their fetus. Seizures, particularly tonic-clonic seizures, can increase the risk of brain or other injuries, congenital malformations, and developmental delay in the fetus. Rarely, they increase the chance of stillbirth or miscarriage. Some women may not have planned for pregnancy and may desire to change their AED once they discover that they are pregnant. However, it is generally not recommended that the particular AED
be changed to another during pregnancy. The overlap of medications while one is being tapered and the other introduced could be harmful to fetal development.

In some studies women with epilepsy have an increased risk for pregnancy-related complications including vaginal bleeding, hypertension, preeclampsia, antepartum hemorrhage, and cesarean delivery. An increase in nausea may interfere with willingness or ability to take oral medications. Other studies have found that appropriate preconception, pregnancy, labor, delivery, and post-delivery care reduce most of these risks to equal that of the nonepileptic population. One large study found an increase in hypertension in the WWE compared with the general population, although there was no significant increase in the number of women with preeclampsia. Even with improvements in the most recent studies, higher-than-expected rates of preterm delivery, failure to progress, and cesarean section are still evident in WWE.

**Fetal and Post-partum Risks Associated with Epilepsy**

Women with epilepsy are more likely to miscarry than women in the general population (36% on AEDs, 19% no AEDs, 13% controls). Stillbirth, defined as fetal death at more than 20 weeks of gestation, has been reported in more WWE (1.3% - 14%) compared to the general population (1.2% - 8%). Status epilepticus poses risks for both maternal and fetal survival, emphasizing the importance of maintaining excellent seizure control, especially complex partial and tonic-clonic seizures, and continuing recommended AED regimens during pregnancy.

**Need for Folate Supplementation (especially if patient is taking any enzyme-inducing drug)**

Folate is a water-soluble coenzyme that occurs naturally in food. Green leafy vegetables, dried beans and peas, and many other types of vegetables and fruits provide folate. In addition, fortified foods are a major source of folic acid. Foods such as some ready-to-eat cereals are fortified with 100% of the RDA for folate. Even so, most women do not consume enough folate in their diet. Folic acid is the synthetic form of folate that is provided in supplements and added to fortified foods. Folate helps produce and maintain new blood cells and is necessary for proper central nervous system development. This is especially important during periods of rapid cell division and growth such as early in the first trimester of pregnancy.

Folate deficient women who become pregnant are at greater risk of giving birth to low birth weight, premature infants. Folate deficiencies have been implicated in the development of certain birth defects, particularly neural tube defects (NTDs). Current recommendations suggest that women contemplating pregnancy and taking an AED
should be given a folic acid supplement. The neural tube closure occurs at about day 26 of pregnancy, often before a woman is aware that she is pregnant. Neural tube and cardiac defects occur in the first 28 days following conception, so folate supplementation should begin before conception is attempted and continue throughout the pregnancy. If the folic acid supplement is begun more than 30 days after conception, it will not provide protection against a neural tube defect. Since 40%-50% of pregnancies are not planned, it is reasonable to recommend routine use of a folate supplement for any women of childbearing age considered to be at risk for pregnancy.

Folate supplementation raises the blood folate levels and is protective for developing fetuses in the general population. Evidence is mounting that folic acid protects developing fetuses against NTDs, but not all of the research supports this conclusion. There have been studies that have failed to demonstrate a neuroprotective effect for periconceptional folate supplementation, but these studies have small sample sizes and methodological problems that limit their usefulness in making recommendations.

However, folic acid supplementation may enhance phenytoin metabolism and thus lower phenytoin blood levels putting the woman at risk for breakthrough seizures.

Enzyme-inducing AEDs have been shown to decrease serum folic acid levels by increasing the metabolism of circulating folic acid. Women taking enzyme-inducing AEDs are at increased risk for NTDs. Indeed, women with epilepsy taking an AED who had babies with congenital malformations were found to have significantly lower blood folate levels than nonepileptic women in some studies. While folate supplementation in this population is recommended, it is not yet clear that such supplementation can truly reduce the risk for birth defects.

The appropriate folate dosage is likely to be dependent on a variety of factors including AED/no AED therapy, which AED is taken, maternal age, and other concurrent medications. Current recommendations have been derived from doses used in the various studies where some neuroprotection was demonstrated. For any sexually active woman of child-bearing potential, recommended daily allowances of folic acid have been increased to 400 μg/day for nonpregnant women, 600 μg/day for pregnant women and those contemplating pregnancy, and 500 μg/day for lactating women. Many epileptologists recommend higher doses (800 μg to 4 mg/day) for women with epilepsy. In most cases, folate intake should not exceed 1000 μg daily to avoid provoking seizures or masking the hematologic effects of vitamin B12 deficiency and pernicious anemia. However, for women with a family history of a neural tube defect, 4.0 mg/day is the recommended dosage and vitamin B12 levels are checked.
Selected References


**AEDs During Pregnancy**

AED treatment should be optimized prior to pregnancy. Seizure control with the minimum effective AED dose is the goal. The ideal treatment of women with epilepsy (WWE) during pregnancy involves achieving an optimal balance between maintaining seizure control and minimizing fetal exposure to AEDs. Monotherapy is preferable to polytherapy for WWE whenever possible, while still maintaining good seizure control. While there are some differences in possible teratogenicity of the various AEDs (see section below), the most effective AED for the particular patient’s seizure type or syndrome should be used. In most cases, AEDs should not be withdrawn or changed during pregnancy. Patients should be cautioned NOT to make any changes in their regimen without a neurology consultation. Most existing guidelines agree on these major points regarding pharmacologic treatment of epilepsy.
Teratogenesis

Some AEDs have been found to be teratogenic, with anatomic and/or behavioral sequelae. There may be minor anomalies, which don’t threaten health, or major malformations. Some of the minor anomalies reported include distal digital and nail hypoplasia and midline craniofacial anomalies such as cleft lip or palate. For many babies, the digital and some craniofacial anomalies may be outgrown by the age of 5.

Reports of major malformations vary widely between studies, likely due to differences in study populations, outcome criteria, assessment methods, and variables such as length of exposure to an AED, AED dosage, or type of epilepsy being treated. This may account for the discrepancies in reports of malformations for individual AEDs. Most major and minor malformations have been reported with the older AEDs such as phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PBT), and sodium valproate (VPA), largely because they are the most widely used AEDs globally. Barbiturates have been found to be associated with major congenital malformations. PHT has been associated with facial clefts, congenital heart defects, and urogenital defects. There have also been reports of dysmorphic facial features and distal phalangeal hypoplasia with PHT. CBZ has been associated with neural tube defects (NTDs), heart defects, hypospadias, hip dislocations, and inguinal hernia. PHT, CBZ, and PBT are folic acid antagonists, so that their teratogenicity may be attributable to their induction of folic acid deficiency. However, addition of folic acid supplementation did not eliminate urinary tract, cardiovascular, and oral/facial malformations in some infants exposed to these AEDs in utero.

VPA is indicated for all forms of epilepsy and is among the treatments of choice for primary generalized epilepsy. Individual studies and data from several pregnancy registries appear to indicate that VPA is more likely than other AEDs to be associated with congenital malformations. VPA has been shown to carry a high risk for spina bifida aperta, cardiovascular complications, urogenital malformations, and skeletal defects. VPA association with congenital defects is dose dependent and is most likely when VPA is used as polytherapy and as monotherapy above doses of 1000 mg/day. In the past several years, prescribing trends have changed, with lower doses of VPA recommended. It should also be emphasized that even in the case of VPA, while the relative risk for malformations may be elevated; the absolute risk is still small. In addition, family history of birth defects may have been present in some women treated with VPA. More than 90% of pregnancies in WWE will result in a normal outcome.

Cognitive and behavioral development is becoming an area of increasing concern with respect to AED treatment. One large retrospective study of cognitive outcomes in children born to women with epilepsy found that the verbal IQ of the children was significantly affected by seizure frequency during pregnancy as well as by maternal IQ. This study also found an independent effect of AED exposure to the developing fetus.
Children exposed to monotherapy valproate (VPA) had a mean verbal IQ that was significantly lower than unexposed children. The effect of VPA was dose dependent. The percentage of children with mental retardation in the general population is 2.5%. In this study, the percentage of children ages 6 to 16 years with mental retardation defined as verbal IQ <70 was 7% in unexposed children, 8% in the CBZ monotherapy group and 22% in the VPA monotherapy group. Other studies support these results. It should be noted that the response rate in this retrospective study was quite low and that the small number of prospective studies conducted to date have had very few children exposed to VPA. For example, a recent prospective, controlled, population-based study looking at intelligence had 86 children with CBZ exposure but only 13 with VPA exposure.

Prospective studies are needed to control for potential confounding variables such as maternal and paternal IQ and maternal congenital abnormalities/genetic issues that may have substantial influence on these results. These variables have been absent from most studies linking AEDs and cognitive and/or behavioral development.

Knowledge about the effects of the newer generation of AEDs is incomplete. Data to date on gabapentin, oxcarbazepine, pregabalin, tiagabine, and topiramate are very limited, but there are no strong negative signals at this point. While some birth defects have been reported with each of the drugs, most have been in situations of polytherapy. Lamotrigine has the most data available at this time, primarily from the Lamotrigine Registry and the UK Epilepsy and Pregnancy Registry. A 12-year international observational study of lamotrigine (LTG) found no substantial increase in overall risk of major defects. Other studies have confirmed these conclusions; however, sample sizes have been small. Data are emerging that higher dosages of lamotrigine may present higher risks to the fetus than lower dosages. When LTG and VPA are given together, there is a higher frequency of major malformations. Emerging data from a pregnancy registry suggest an association between LTG and non-syndromic oral clefts, with a rate of cleft lip/palate 24 times greater than the expected rate. Data regarding zonisamide are quite limited, but malformations recorded to date raise some concerns with respect to this AED.

There have been very few pregnancy outcomes reported with levetiracetam (LEV), but it has been speculated that LEV may have a favorable profile for pregnant women because it has <10% protein binding and is eliminated primarily via renal excretion and extrahepatic hydrolysis. Renal blood flow increases in early pregnancy and persists throughout; LEV elimination has been found to be enhanced with this increased renal blood flow. Preliminary studies have found a good pregnancy safety profile with this AED; however, data are needed before it can be said to be non-teratogenic. Neonatal drug clearance was complete within the first few weeks of life.
**Prenatal Screening**

Prenatal screening to detect major and minor fetal malformations will permit preparation for adequate care for the neonate, particularly for neural tube defects and cardiac defects.

The following prenatal testing is recommended to determine any anomalies in the developing fetus:

- First trimester ultrasound at 11 – 13 weeks is recommended to rule out neural tube defects and other major malformations.
- Maternal serum alpha-fetoprotein at 16 weeks is another screen for neural tube defects.
- Second trimester ultrasound at 18 – 22 weeks to determine cardiac development, head and spine anatomy, and minor malformation of the face such as cleft lip or cleft palate. Fetal cleft lip detection is best determined at 20+ weeks. A level 2 ultrasound will screen for major malformations.

Surgical intervention immediately after birth may be indicated, and there are some prenatal interventions that are possible. Studies have found that a majority of parents with knowledge of facial anomalies are better prepared following prenatal counseling. Some patients may consider therapeutic abortion if a major malformation is detected.

**Labor and Delivery**

Most (about 95%) WWE have a safe vaginal delivery, without a seizure during or in the 24 hours following delivery. Women with primary generalized epilepsy are more likely than those with partial epilepsy to have a seizure at this time. Sleep deprivation can provoke a seizure so that in some cases obstetric anesthesia may be indicated prior to delivery. WWE are more likely than the general population to have labor induced, although epilepsy is not an indication for induction. This may be related to the benefits of stress reduction to avoid precipitation of seizures or it may be related to weak uterine contractions. Abruptio placenta (separation of the placenta from the uterine wall) may occur more frequently in WWE. Cesarean sections and mechanically assisted delivery are also more common in WWE.

It is important to remind WWE to bring their AEDs to the hospital during labor and to take regular doses during this period under the supervision of hospital staff. Intravenous (phenobarbital, valproate, levetiracetam) or intramuscular (phenytoin, phenophénytoïn) administration may be needed if the woman is not able to keep down oral medication.
**Vitamin K recommendations**

It is suggested that oral vitamin K supplementation at 10 - 20 mg/day be prescribed during the last month of pregnancy for women with epilepsy (WWE). This is particularly important for women taking enzyme-inducing AEDs. Some AEDs, including carbamazepine, phenobarbital, primidone, ethosuximide, phenytoin, and vigabatrin have been associated with alterations in vitamin K metabolism that induce a deficiency in the fetus, predisposing to a bleeding disorder. Vitamin K is recommended for all neonates at birth; however, neonates born to WWE should be monitored for bleeding even though some studies do not demonstrate an increased risk of bleeding for these babies. The recommended dosage for neonates is 1 mg IM or IV at birth. If a woman has not taken Vitamin K before beginning labor, it can still be administered during labor.

**Postpartum Care and Breastfeeding**

AED levels should be monitored closely in the weeks following delivery. During this period AED levels may increase gradually. The increase in postpartum plasma levels for EIAEDs starts about 10 -14 days postpartum. The drugs that are excreted renally such as levetiracetam and oxcarbazepine and those affected by estrogen, such as lamotrigine, show elevated levels with days of delivery. Thus some women will require a dose adjustment immediately following delivery. A small study suggests that oxycarbazepine levels should be monitored during pregnancy and immediately following delivery. Depending on the AEDs used during labor and delivery, both mother and neonate may experience some lethargy. Newborns, particularly infants born prematurely, may have limited capacity to metabolize phenobarbital for several days following delivery. The neonate may be irritable and have feeding problems if benzodiazepines and/or barbiturates were used.

Most infants of WWE are able to breastfeed successfully. Breastfeeding benefits to the mother and infant outweigh any risks from AED exposure. AED concentrations in breast milk are far less than they are in maternal serum; however, the serum half-life of AEDs is longer in the neonate than in the mother. Parents should be advised to be alert to any increases in lethargy and to stay in close touch with their pediatrician in such cases. When the baby is born, an appointment for a neurological evaluation should be made for age 4-6 weeks.

**Parenting Issues and Safety**

WWE need to organize their lives to minimize fatigue in the weeks following delivery in order to minimize the occurrence of seizures precipitated by fatigue. They may also be at increased risk for breakthrough seizures due to stress. Mothers should be encouraged to
nap when their baby naps, though this may not be possible if there are other children at home. Asking for help from other adults can alleviate some of the stress, and provision for another adult to do nighttime feedings can help with fatigue. For women who are breastfeeding, this can be accomplished with either expressed breast milk or with supplementary formula.

Each woman needs to assess her particular seizure pattern, and then to make appropriate arrangements for her own safety and that of her baby. For example, if her pattern is to fall during seizures, she may wish to rely on a stroller or carriage in the house rather than carrying the infant. If she tends to drop things, perhaps a baby harness is appropriate. Baby care such as changing diapers and clothing can be done on a blanket on the floor rather than on a high changing table, especially during the immediate postpartum period when AED levels fluctuate. A second person should be present during baths to avoid the danger that even a momentary lapse in alertness can present.

Selected References


WOMEN BEYOND CHILDBEARING YEARS

Menopause, Definitions

Menopause is a time of life not yet well researched for women with epilepsy. There are no prospective studies; available information is derived from clinical experience and retrospective studies generally based on self-report questionnaires. Nevertheless, it is important for clinicians to consider the effects of epilepsy on menopause and the effects of the hormonal changes associated with menopause and with hormonal replacement therapy (HRT) on seizure activity. Understanding the changes in seizure control that might occur beginning with perimenopause is becoming increasingly important. As the worldwide population ages, women who have reached menopause and the large group of women approaching menopause constitute one of the fastest growing segments of society. These women will live up to one-third of their lives beyond the onset of menopause and research is needed to determine the best therapeutic and lifestyle choices for them.

Earlier in this Discussion Guide, we presented evidence that female sex hormones and their fluctuations can influence seizures in women with epilepsy. Estrogen has been found to have a seizure-promoting effect, while metabolites of progesterone have an anti-seizure effect. Progesterone withdrawal at the end of the luteal phase just preceding or during the onset of menstruation can exacerbate seizure activity. The substantial effects of these hormones on seizure control during other phases of a woman’s reproductive life suggest that perimenopause and menopause will produce changes in the natural history of seizures.

A working definition of menopause is a full year of amenorrhea during which estrogen and progesterone stabilize at low levels. The perimenopausal period is characterized clinically by irregular menses, with increasing months of missed periods, the experience of "hot flashes" or vasomotor symptoms for some women, and mood changes. During the perimenopause period, circulating estrogen levels decline gradually, and cyclical luteal phase progesterone surges also decline. The estrogen/progesterone ratio in perimenopause rises and becomes generally unpredictable, whereas during menopause the ratio of low levels of these reproductive hormones is stable. These differences suggest that perimenopause will be associated with an increase in seizure activity. The limited amount of research in this area does show seizure exacerbation during perimenopause, which is even more pronounced for women who have had a history of a catamenial seizure pattern. Predictably, the fraction of the group of women with epilepsy reporting a catamenial increase in seizure frequency is considerably lower during menopause than during perimenopause.
Onset of perimenopause is highly variable, best predicted by the age of onset in the woman’s mother. There is some evidence that menopause starts earlier for women with epilepsy, but it is not known whether this is related to use of enzyme-inducing AEDs or other factors.

**Perimenopause and Epilepsy**

Perimenopause is a difficult time for any woman, but women with epilepsy face unpredictable patterns of estrogen and progesterone changes. This complex phase could last for several years, with correspondingly lengthy effects on seizure patterns.

With menopause, cessation of swings in estrogen and progesterone levels should reduce cyclical exacerbations that might have occurred with catamenial epilepsy. Loss of estrogen removes the potential for enzyme inducing interactions with AEDs as well as its epileptogenic effect on the brain. However, the loss of progesterone removes its protective effect that might have reduced seizures.

**Early Menopause with Epilepsy**

The low estrogen levels that are a part of menopause affect many different organ systems in the body. These changes generally occur slowly and differ for each woman. While estrogen levels decrease, progesterone levels also decrease in menopause. Other hormonal, endocrine, and metabolic changes that occur during menopause can also influence the risk of seizures. This makes it difficult to predict what to expect for any individual woman. While there is some variation, menopause generally occurs between the ages of 48 and 55 years. More recent data suggest that women who have had epilepsy throughout their adult lives tend to cease menstruation about 3 years earlier than women in the general population. Most reports have not differentiated between effects of epilepsy and of seizure and the effect of AEDs on the decline in hormonal activity.

One investigation of women with epilepsy age 45 years and older was designed to try to study these as discrete components of ovarian failure. This study found a rate of premature ovarian failure higher than that of the general population. Lifetime total number of seizures and perhaps seizure frequency and duration of epilepsy appear to be correlated with age at menopause.

Women report that menopause seems to influence their seizures. In one study published in 1999, 67% of women with epilepsy self-reported changes in their seizure frequency with menopause. For 27%, seizures lessened or improved, but for 41%, they became worse. The reduction in seizures was particularly prominent for women who experienced catamenial epilepsy during their reproductive years; 69% of these women reported an
improvement in their seizures during menopause. There is some evidence that women going through menopause may be at greater risk for developing epilepsy. In this study, 20% of women actually begin having seizures for the first time after the onset of menopause. Another small study presented similar figures, with 60% of women reporting that their seizures did not change in frequency or improved with the onset of their menopause. About 30% reported some improvement in their seizure frequency while approximately 40% reported that their seizures became more frequent in menopause.

**Hormone Replacement Therapy**

Similar to women in the general population, many women with epilepsy will weigh the risks and benefits of hormone replacement therapy (HRT) as they approach menopause. Some women may not wish to use HRT because of risks associated with this therapy. For women with epilepsy, HRT’s contribution to protection against osteoporosis may be a benefit worth considering.

HRT is available in many forms including estrogen alone, combined estrogen with progesterone, and combinations that include testosterone. Estrogen without progesterone may provoke seizure activity, so that option is not recommended for women with epilepsy. Testosterone is a precursor to estrogen so it is not likely to reduce seizures.

For women with epilepsy, HRT with estrogen can influence antiepileptic metabolism and seizures. There is no convincing evidence at this time to support the view that HRT worsens seizures. Women should not necessarily be denied the benefits of HRT because of unproven concerns that it may worsen their seizures. Nonetheless, women starting HRT should be monitored and AED treatment should be adjusted as needed.

Hormone replacement therapy (HRT) in menopause or the perimenopausal period is in less favor currently but has demonstrated benefits in prevention of osteoporosis and improves vasomotor symptoms. The effect of HRT on seizures is unclear. This uncertainty may be partly due to the varied formulations of HRT, including unopposed estrogens or mixed estrogen/progesterone treatments.

**Bone Health**

Women with epilepsy may have an additional risk factor for osteoporosis, beyond their increased risk due to the earlier onset of menopause. Earlier onset of menopause in women with epilepsy affects their health by accelerating the age at which they are vulnerable to bone loss and to a decrease in cardioprotective lipid metabolism. Possible health consequences need further exploration.
Women with epilepsy are at increased risk of fractures, osteopenia, and osteoporosis. Excessive bone loss can cause osteoporosis. This puts a woman at major risk for broken bones and serious fractures. For women who may fall when having a tonic-clonic seizure or as a result of dizziness or sedation related to medication, this becomes a particularly serious problem. Osteoporosis is a particular problem for menopausal women. Some antiepileptic medications may be associated with mineral loss from bone, osteoporosis, and other related problems. Prevention includes a diet high in calcium and vitamin D, and adequate exposure to sunlight. Cholecalciferol may be prescribed to enhance calcium uptake, particularly for women taking enzyme-inducing AEDs. In addition, physical exercise increases bone mass before menopause and slows bone loss after menopause. HRT with estrogen also prevents osteoporosis and is a major reason for menopausal women to consider HRT. Bone mineral density measurement (DEXA scan) or a urinary bone marker test is needed to determine whether a woman has sustained excessive bone loss. Some AEDs may promote bone loss, leading to osteoporosis because of hepatic microsomal enzyme induction, producing vitamin D catabolism. This is a major mechanism resulting in bone loss. This independently predicts an increased risk of fractures for women with epilepsy. This increased risk results from the effect of enzyme-inducing AEDs on vitamin D, which is added to the natural risk of osteoporosis from postmenopausal status. Tonic-clonic seizures also increase the risk of falls and fractures. While the mechanism or mechanisms of accelerated osteoporosis secondary to AED use are not well understood and are under active investigation, a number of AEDs are implicated in promoting accelerated vitamin D metabolism, leading to bone loss, including: phenobarbital, primidone, phenytoin, carbamazepine, oxycarbazepine, and valproate. A pattern of changes in bone biomarkers suggestive of secondary hyperparathyroidism is seen in women with epilepsy taking carbamazepine and in a small study oxycarbazepine, so that these women should be prescribed 25-hydroxyvitamin D replacement. It is currently believed that additional mechanisms (e.g., direct effects on bone cells, impaired calcium absorption) are also being studied to find an explanation for the osteopenia associated with non–enzyme-inducing medications such as valproate. Long-term data on most of the newer AEDs are too limited to draw definitive conclusions but it is expected that the pharmacologic properties of some newer AEDs may prove to be safer with respect to bone health.

Prevention and treatment strategies for AED-related bone loss vary and are revised as new information becomes available. For patients taking the older AEDs (phenobarbital, primidone, phenytoin, carbamazepine, valproate), it is recommended that at least 1000 mg of calcium/400 IU vitamin D daily be taken by premenopausal women and 1500 mg calcium/600 IU vitamin D daily be taken by postmenopausal women. This is recommended for all women, not only women with epilepsy, but is particularly urgent if enzyme-inducing AEDs are being taken. Higher doses of supplements are suggested by some researchers. Calcium supplements may decrease the absorption of phenytoin, so that levels need to be monitored closely when women begin taking supplements. Even high-dose supplementation may not provide sufficient protection for women taking
strong hepatic enzyme inducers, such as phenytoin and phenobarbital. One of the newer, non–enzyme-inducing AEDs may be preferable for older women. In patients with known osteoporosis, treatment with bisphosphonates should be considered, although the long-term effects of these formulations are not yet known. The declining enthusiasm for HRT should shift the recommendation to a bisphosphonate; however, the main emphasis for women should be on calcitrol with vitamin D3 supplementation.

**Age and AEDs**

As people age, their drug treatment may become more complex and must always be examined across all medications and health factors. Seniors are especially sensitive to the sedating and potential adverse cognitive effects of medications such as AEDs. In addition, they are increasingly likely to have health problems requiring medications that can interact with their AEDs. Some AEDs with faster or slower clearance rates may not work as expected; they may also produce unanticipated toxic reactions. A prospective study with more than 9,700 elderly community-living women found that continuous AED use is associated with increased rates of bone loss at the calcaneus and the hip. This rate of bone loss, if unchecked, is sufficient to lead to an increased risk of hip fracture of 29% over 5 years in women age 65 years and older.

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PHYSICIAN'S DISCUSSION CHECKLIST FOR WOMEN WITH EPILEPSY

This Discussion Checklist was developed by the Epilepsy Therapy Development Project http://www.epilepsytdp.org to help physicians treating women with epilepsy. The issues were reviewed by a panel of epilepsy experts:

For All Women, Adolescents, & Pre-Teens During Reproductive Years

- Relationship between hormones & epilepsy (overview)
- Possible menstrual cycle-related influence on seizure susceptibility (catamenial epilepsy)
- Impact of epilepsy on sexual & on reproductive issues
- Epilepsy is rarely related to infertility; (consult infertility specialist if there is a sign of difficulty conceiving test for PCOS)
- Relation of some AEDs to libido and potency problems
- Women with epilepsy CAN become pregnant with or without AEDs; importance of careful pregnancy planning including folate supplementation
- Need for effective & consistent contraception to avoid unplanned pregnancy
- Effective contraception choices (interactions between hormonal contraception & certain AEDs; possible contraceptive failure and need to consider barrier method for added protection)
- Other forms of contraception (patch, IUD, Depo Provera®)
- Need to inform neurologist if contraception is discontinued
- Need for calcium supplementation and vitamin D for bone health

Physician’s Signature       Patient’s Name & Signature       Date of Discussion
Women Planning to Conceive

*Note: Confirm the diagnosis of epilepsy & seizure type. In all discussions, emphasize the balance of all risks & the goal of controlling seizures*

- Healthy pregnancies & healthy babies are the goal
- Need for optimum seizure control
- All risks (women not taking AEDs also have risks)
- Risks to the baby from AEDs must be balanced with risk of seizures to baby & mother
- Ways to reduce risks to mother & baby (eg, AED choices; folate supplementation)
- Appropriate AED medication/need to optimize before pregnancy; importance of NOT making any changes without neurology consultation (maintaining good compliance)
- Identify an obstetrician comfortable treating a woman with epilepsy
- Need for folate supplementation (especially if patient is taking any enzyme-inducing drug)
- How pregnancy can affect seizure frequency & severity
- Fertility treatments & possible effects on AED levels & seizure susceptibility

______________________________  ________________________  ________________________
Physician’s Signature          Patient’s Name & Signature  Date of Discussion
**Pregnant Women**

Note: Confirm the diagnosis of epilepsy & seizure type. In all discussions, emphasize the balance of all risks & the goal of controlling seizures

- Consultation with patient’s obstetrician ____________________________ (date)
- Possible teratogenic effects compared to people not taking an AED
- Possible changes in AED therapy (only in consultation with neurologist)
- For patients requiring multiple AEDs for seizure control, discussion of choices, risks, & need for close monitoring of AED dose & blood level
- Vitamin K recommendations for mother before delivery & for baby
- Need to bring AEDs to the hospital during labor and to take regular doses
- AED dose adjustment following delivery and post-partum follow-up
- Breastfeeding/safety for the newborn
- Newborn appointment for neurologist evaluation (age 4-6 wks)
- Parenting issues to maximize safety for the newborn including minimizing mother’s fatigue to avoid seizure exacerbation & home safety preparations
- Have ultrasound first and second trimester

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**Women Beyond Childbearing Years**

- Bone health & need for calcium supplementation & bone density monitoring; seizure control to prevent falls
- Peri-menopause effects on seizures/AEDs
- Menopause/hormone replacement issues; enzyme-inducing effects of hormones on AEDs