Contraception and prenatal vitamin supplementation for women on antiepileptic medications

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ABSTRACT

This article identifies interactions among AEDs with hormonal contraceptives and summarizes management strategies from the literature. Recommendations for addressing folate, vitamin K, and vitamin D deficiency caused by AEDs are also reviewed.

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Antiepileptic drugs (AEDs) are used for epilepsy, mood disorders, anxiety, migraines, and chronic pain. This multitude of uses exposes an increasingly wide range of women in their child-bearing years to clinically important drug interactions and side effects.

Some medications, in particular the enzyme-inducing AEDs (EIAEDs), can decrease serum levels and potentially the effectiveness of hormonal contraception methods, putting many women at risk for contraceptive failure. This may be further complicated by potential teratogenicity. Folate and vitamin K deficiencies in otherwise healthy women may be caused by AEDs and should be addressed during preconception counseling.[1] Given that over half of pregnancies may be unplanned,[2] the importance of this extends beyond those who are planning to become pregnant. Vitamin D levels and calcium can also be affected and are important in women of all ages.

This article will identify the interactions among AEDs with hormonal contraceptives and summarize management strategies from the literature. Recommendations for addressing folate, vitamin K, and vitamin D deficiency caused by AEDs are also reviewed.

Abbreviations: AED = Antiepileptic drug, COC = combined oral contraceptive, EIAED = Enzyme inducing antiepileptic drug, EE = ethinyl estradiol, LNG = levonorgestrel, LNG-IUD = levonorgestrel-releasing IUD, OC = oral contraceptive

INTERACTION WITH HORMONAL CONTRACEPTIVES

Certain AEDs have the capacity to induce CYP3A hepatic enzyme activity and increase metabolism of many drugs, including ethinyl estradiol (EE) and progestins[1,3-5] (Table 1). The effect can result in 50% or more reduction in serum levels of these hormones and is subject to inter-individual variation.[6] This can lead to decreased effectiveness of combined oral contraceptives (COCs), combined contraceptive patch (Ortho Evra) and vaginal ring (NuvaRing), progesterone only pills (POPs), progesterone implants, and emergency contraceptive pills (Plan B, Next Choice). This interaction can continue for 4 weeks after the AED is discontinued when hepatic enzymes return to pre-induction levels.[5,6] Phenobarbital, phenytoin, and carbamazepine have also been shown to cause increases in sex hormone-binding globulin (SHBG) leading to a reduction in free plasma progestin levels, possibly contributing to contraceptive failure.[3,4]

Contraceptive methods not affected by EIAEDs include depot medroxyprogesterone acetate injection (DMPA, Depo-Provera), levonorgestrel-releasing IUD (LNG-IUD, Mirena), copper containing IUD (ParaGard), and barrier methods.[3-7] These options should be considered a first choice in women on interacting AEDs who want to avoid any risk of decreased contraceptive effectiveness due to this interaction.[5,6]

The metabolism of DMPA is dependent on hepatic blood flow and has near 100% first pass effect, which will not be altered by additional enzyme induction.[6] During the initial months (and in the absence of EIAEDs), DMPA can commonly cause irregular menstrual bleeding and spotting which may be misinterpreted as a sign of contraceptive failure.[2] This effect decreases with continued use and usually does not require intervention. Nevertheless, some authors have recommended decreasing the dosing interval from every 3 months (13 weeks) to every 10 weeks in the presence of

EIAEDs.[3,8] This contraceptive may not be preferred by women who plan to become pregnant within 1 to 2 years due to possible delayed return to fertility, or because of concerns with adverse effects on bone density with long term use, weight gain, skin problems, and mood symptoms.[2,7] Despite the apparent lack of interaction with DMPA, use of progesterone implants, such as the etonogestrel implant (Implanon, Nexplanon) and levonorgestrel implant (Norplant, off market), with EIAEDs have had various reports of high failure rates, and are not recommended.[3,4,6,7] The LNG-IUD produces high progestin concentrations locally and has not been shown to have any significant decreased effect from EIAEDs.[3-8]

If the unaffected contraceptive methods are not desired or appropriate, higher doses of an estrogen containing COC may be considered. Use of a COC containing at least 50mcg of EE with a progestin, as found in Zovia 1/50 or Ogestrel, is recommended.[3,5,6,8,9] This may also be achieved using an off-label combination of COCs containing 30mcg and 20mcg EE (ie, one tablet each of Levora and Aviane), or two 30mcg tablets (ie, two tablets of Levora), as long as the progestin is the same.[5,6] An even higher dose of EE may be indicated if breakthrough bleeding occurs with 50mcg EE.[3,8] Increased side effects from high doses of estrogen should not be expected, since the combination with an EIAED would decrease plasma EE levels.[6] It should be noted that mestranol, a prodrug for EE, provides plasma levels similar to those produced by administration of 35mcg EE, the contraceptive effect of which would be inadequate in the presence of an EIAED.[6,10]

Even with use of high dose COC regimen, there remains the possibility of contraceptive failure. Women may be encouraged that failure rates of high dose COC with EIAEDs is still lower than barrier methods alone (~7% vs 15-20%[3]), although higher than COC use in the absence of this interaction (5% with typical use[11]). If more effective contraception with COC use is desired, then additional backup methods such as condoms and spermicidal gel are recommended.[3,5] Tricyling, which involves taking 3-4 cycles of high dose OC followed by a shorter pill-free interval of 4 days, has been suggested as a method to limit the possibility for decreased anovulatory effect occurring during the pill-free interval.[6,8] This practice has not been supported by evidence that it improves contraceptive efficacy[5], but could be considered. Breakthrough bleeding occurring mid-cycle may be a sign of loss of contraceptive effectiveness, and additional backup methods should be used. Women should be encouraged to report this effect.[1,3]

Table 1 summarizes individual interactions of AEDs on hormonal contraceptives, and recommendations for alternative contraceptive methods.

Table 2 lists AEDs which do not produce any significant decrease in hormonal contraceptive effectiveness.

There is also an interaction of hormonal contraceptives on the efficacy of some AEDs, which may potentially lead to loss of seizure control or reduced effectiveness in other indications.[4,6,7,21,23,24] Increased clearance of valproate and lamotrigine occurs, and changes in benzodiazepine levels may be seen. An increase in phenytoin levels with resulting toxicity has also been reported.[13]

Table 3 summarizes AEDs which may be affected by hormonal contraceptives and recommendations on monitoring and management.

The interaction between lamotrigine and COCs causes concerns for both medications. It is generally accepted that lower doses of lamotrigine do not alter COC efficacy, although there has been suggestion that this may not apply to higher doses.[20] The estrogen component of contraceptives, including patch and vaginal ring formulations, induce glucuronidation of lamotrigine.[6,7,21] This can lead to decreased serum levels and breakthrough seizures. However, initiation of estrogens do not significantly add to this effect when lamotrigine levels are already decreased by concurrent use of other EIAEDs.[6] Elevated lamotrigine levels occurring during the pill-free interval with COCs have contributed to increased side effects. Therefore, shortening the pill-free interval or using extended or continuous cycle regimens may be considered.[6] Monitoring serum levels and/or evaluating for increased side effects should also be considered when COCs are discontinued.

The LNG-IUD and progesterone implant are not expected to either be significantly affected by or cause altered levels of lamotrigine.[6,7] These methods, the copper containing IUD, and DMPA are preferred to avoid fluctuations in lamotrigine levels or any decreased contraceptive effectiveness. Based on data with lower lamotrigine doses[22], it may be reasonable to assume contraceptive efficacy of normal dose COCs with lower doses of lamotrigine while monitoring for breakthrough bleeding.

FOLIC ACID SUPPLEMENTATION

Folate deficiency can occur due to treatment with AEDs and may contribute to teratogenic effects such as neural tube defects (NTDs).[25] The neural tube closes by 29 days after conception, often before pregnancy is realized, thus

Table 1. Medications that Decrease Hormonal Contraception Effectiveness

Drug	Interaction summary	Alternative Contraceptive Recommendations
Carbamazepine	Induces hepatic enzymes = increased metabolism of estrogen and progestin hormones Decreased EE levels 6-66% and LNG 29-57%[12] Report of pregnancy with etonorgestrel implant[4]	Long acting methods Medroxyprogesterone acetate depot injection (Depo-Provera). Increased frequency every 10 weeks rather than every 3 months may be considered[3,8] but is not necessary[6] Levonorgestrel-releasing IUD (Mirena) Copper containing IUD (ParaGard) Barrier methods Condoms, female condoms, diaphragm, contraceptive sponge COC with at least 50 mcg EE. Consider increase to 75-100 mcg EE if breakthrough bleeding occurs[3,8] Tricycling (or extended cycle) regimens may be considered[6,8] Mestranol 50 mcg is not recommended[6,10] Contraceptive failure may still occur.[9] Additional barrier methods or spermicidal gel are recommended[3,5] Emergency contraceptive- no studies on dose effectiveness. Recommendations have been made: Two 1.5mg LNG tablets (3mg total) single dose given stat, within 72 hours of unprotected intercourse.[6] Consider insertion of copper containing IUD, which is unaffected by EIAEDs[5] Alternative or backup contraceptive methods should be continued for 4 weeks after interacting AED is discontinued[6,5]
Clobazam	Dose dependent CYP 3A4 induction Effectiveness of hormonal contraceptives may be decreased[13]	
Eslicarbazine	1200mg/day has been shown to reduce plasma concentrations of OCs[14]	
Felbamate	May induce CYP3A4 Significantly decreased AUC 42% for gesterone. Non-significant decrease in EE AUC. One report of breakthrough bleeding[15] Higher estrogen component recommended if COC used[3]	
Oxcarbazepine	Induces hepatic enzymes = increased metabolism of estrogen and progestin hormones 600mg/day decreased AUC of EE 47% and LNG 47%. One report of breakthrough bleeding[16] 900mg/day decreased AUC of EE 48% and LNG 32%[17] Reduced efficacy of COC should be anticipated[3]	
Phenobarbital	Induces hepatic enzymes = increased metabolism of estrogen and progestin hormones Decreased EE and norethindrone concentrations and breakthrough bleeding have been reported[3] Pregnancy reported with levonorgestrel implant[4]	
Phenytoin	Induces hepatic enzymes = increased metabolism of estrogen and progestin hormones Pregnancy reported with levonorgestrel implant[3,4] Average 50% decrease EE and LNG in 6 patients receiving phenytoin 200-300mg/day[3] Significantly decreased AUC of EE and LNG[12]	
Primidone	Induces hepatic enzymes = increased metabolism of estrogen and progestin hormones Pregnancy reported with use of COC[4]	
Rufinamide	Weak CYP 3A4 inducer may increase metabolism of estrogen and progestin hormones Decreased C_{max} and AUC of EE and norethindrone[13]	
Topiramate	Moderate CYP 3A4 inducer 50-200mg/day did not significantly affect AUC of EE and norethindrone[18] 200-800mg/day caused dose related decrease in EE AUC by 18-30% due to increased oral clearance.[19] Norethindrone clearance was not significantly changed	Alternative contraceptive recommendations considered for doses > 200mg/day due to dose dependent increased EE clearance. OC with ≥ 35mcg EE recommended[19]
Lamotrigine (LTG)	LTG 150mg/day did not affect concentrations of EE or LNG[22] LTG 300mg/day caused decreased AUC of LNG 19% and Cmax 12% in one study.[20] 7 of 16 women (32%) experienced breakthrough bleeding, although there was no evidence of ovulation by serum progesterone levels Mechanism of effect on LNG is unknown, possible that lamotrigine induces glucuronidation or has an effect on the hydroxylation and sulphation of LNG[20] Possible some forms of LNG efficacy may be reduced	LNG-IUD (Mirena), Copper containing IUD (ParaGard), DMPA (Depo-Provera), etonogestrel implant (Implanon, Nexplanon) are all effective and do not affect lamotrigine levels[6,7] Monitor for breakthrough bleeding, contraceptive safety cannot be guaranteed especially with higher doses of lamotrigine (≥300mg/day)[7,8] Lower doses (150mg/day) do not affect COC[22] and contraception may be considered as likely effective

Table 2. Medications that Do Not Significantly Decrease Hormonal Contraception Effectiveness[3-7,13,14]

Drug	Interaction information
Benzodiazepines (diazepam, clonazepam, lorazepam)	Do not induce hepatic enzymes
Clorazepate	Does not induce hepatic enzymes
Divalproex, Valproic acid (VPA)	No episodes of breakthrough bleeding in 7 patients on VPA 600-1800mg/day. No significant differences on EE and LNG kinetics, although increase in peak EE concentrations with VPA found.[3]
Ethosuximide	No enzyme inducing properties, unlikely to have significant interactions with COCs. No formal studies available.[3]
Gabapentin	Does not affect hepatic enzymes. 1200mg/day produced small insignificant increases in EE C_{max} and AUC. Does not appear to reduce OC efficacy.[3]
Lacosamide	Up to 400mg/day for 10 days did not affect EE or LNG in one study.[14] 20% increase in EE C_{max} reported, unlikely clinically significant.[13]
Levetiracetam	Does not induce hepatic enzymes. 1000mg/day in 18 patients did not influence kinetics of EE or LNG. Serum progesterone levels indicated ovulation did not occur.[3]
Pregabalin	Interaction studies on healthy subjects showed no effects on pharmacokinetics of OCs.[13]
Tiagabine	Does not induce hepatic enzymes. 2mg/day caused no significant changes in EE, LNG, and desogestrel in 10 patients. Plasma progesterone levels remained in non-ovulatory range.[3]
Vigabatrin	3000mg/day in 13 patients had no significant difference on EE or LNG kinetics; 2 patients did have 50% and 39% decrease in EE AUC. Due to no effects on hepatic enzyme activity, no interaction with COC was concluded.[3]
Zonisamide	No evidence of CYP3A4 induction. No studies on concurrent COC pharmacokinetics.[3]

increasing the importance of folic acid supplementation before conception.[27] It has been suggested that folic acid supplementation may also decrease risk for orofacial clefts.[27] Direct reduction in folate levels up to 90% has been reported with phenytoin, carbamazepine, and barbiturates, while valproic acid has been found to interfere with folate metabolism.[25] Gabapentin, lamotrigine, and vigabatrin do not have reported antifolate effects.[25]

Limited data exists on the effect of folic acid supplementation in women taking AEDs.[8] Most information comes from studies with women who have had a prior NTD affected pregnancy and therefore considered high risk. The recommendations for these women include preconception supplementation with folic acid 4mg/day continuing throughout the end of the first trimester. This dose has been suggested for women on certain AEDs associated with higher risk for NTDs such as carbamazepine and valproic acid.[1,25] Others have recommended folic acid 5mg/day starting 3 months prior to conception and continued throughout the first trimester for women on carbamazepine or valproic acid.[25] Unless they are using a contraceptive, this recommendation has also been made for all women taking AEDs.[8] Serum folate levels may be monitored to ensure adequate supplementation.[25]

Higher doses of folic acid generally have a low risk of toxicity.[26] Caution may be warranted especially for those with epilepsy as folic acid supplementation may induce hepatic enzymes[1,25] and has been shown to decrease levels of phenytoin as well as to increase seizure frequency in patients on phenytoin, phenobarbital, and primidone.[13] AED levels should be checked frequently after adding folic acid, especially in epilepsy.[1,25] Vitamin B12 levels should also be monitored prior to initiating folic acid since supplementation may mask clinically important signs of pernicious anemia.[25]

Folic acid bioavailability decreases with increasing dose, supporting divided doses rather than once daily administration. Three times daily dosing of folic acid resulted in a 25% increase in methyltetrahydrofolate, the biologically active form of folic acid.[27] For example; higher folic acid intake could be achieved with a prenatal multivitamin plus folic acid 1mg TID or 2mg BID.

Standard preconception doses of at least 0.4mg/day of folic acid should be a minimum consideration for women

Table 3. Anticonvulsant Medications Affected by Hormonal Contraception

Drug	Interaction summary	Recommendation
Divalproex, Valproic acid (VPA)	EE component may increase glucuronidation metabolism of total valproate and free valproate 21.5% and 45.2% during co-administration[23] Very low dose, low dose, and patch forms of COCs caused significant increase in mean oral clearance and unbound mean clearance of VPA[4] Serum VPA levels declined 23.4% during active vs inactive pill intake in one study[24] Report of one pt with increased seizure occurrence during active pill (30mcg EE/1mg ethynodial diacetate) compared with inactive pill over 5 month period associated with reduced VPA levels[4]	Normal doses of hormonal contraceptives may be used Monitor VPA levels with initiation or discontinuation of contraceptive[23] VPA level monitoring during pill-free intervals may be be necessary[23]
Lamotrigine (LTG)	Estrogen component induces glucuronidation and may decrease LTG levels 40-60%; levels may possibly double during placebo week[6,7] Vaginal ring (NuvaRing) decreased LTG levels 15-50%[21]	Monitor for increased side effects from LTG during pill-free week[6] Consider normal doses of extended cycle contraceptives to limit LTG level fluctuation during the pill-free interval[6] Monitor serum LTG levels and for breakthrough seizures/increased seizure frequency when starting or stopping estrogen containing contraceptive[13] May need to adjust LTG dose up to 50% when starting or stopping estrogen contraceptive if not on other inducing drugs[6,7]
Clonazepam **Clorazepate**	Oral contraceptive (OC) may decrease the oxidative hepatic metabolism of clonazepam and clorazepate, leading to increased sedation and prolonged CNS depression[13]	Monitor for increased benzodiazepine effect when OCs are added. Lower doses may be needed during concurrent administration of hormonal contraceptives[13]
Diazepam	OC impair diazepam metabolism. In one study, diazepam clearance was 40% less in women on OC[13] Psychomotor impairment was greater on cycle day 28 than on cycle day 10[13]	
Lorazepam	OC may increase glucoronidation of lorazepam and increase its clearance[13]	Women on OCs may require higher doses of lorazepam. Monitor for decreased effectiveness of lorazepam during concomitant administration of hormonal contraceptives[13]
Phenytoin	OC have been reported to increase steady state levels of phenytoin resulting in toxicity[13]	Monitor steady state phenytoin levels when starting or stopping OC therapy[13]

of childbearing age on any AED.[9,26] If planning for pregnancy, higher (4 to 5mg/day) doses should be initiated 3 months prior to conception in women on carbamazepine, valproic acid, phenytoin, and barbiturates, and perhaps higher than standard doses considered for women on other AEDs with monitoring of folate levels taken into consideration.

VITAMIN K SUPPLEMENTATION

Enzyme-inducing AEDs have been implicated in the increased risk for neonatal bleeding when used during pregnancy.[1,9,25] This may be due to placental crossing of the AED causing induction of hepatic enzymes in the fetal liver, leading to increased metabolism of vitamin K.[9,25] Decreased circulating levels of the vitamin K dependent clotting factors increase the risk for hemorrhage in the newborn, which generally occurs during the first 24 hours after birth and may be severe.[1,9,25]

Maternal vitamin K supplementation is recommended when there is exposure to EIAEDs during pregnancy. Doses of oral phytonadione 10mg to 20mg daily during the last 4 weeks of pregnancy have been recommended.[1,9,25] There has been question of the benefit of this strategy due to the poor placental crossing of phytonadione into fetal circulation, although it is reported to have value in preventing neonatal hemorrhage and carries little to no risk with its use.[9,25]

There is general consensus that 1mg of intramuscular phytonadione should be administered shortly after delivery to all newborns exposed to EIAEDs.[1,8,9,2] Intravenous administration should be reserved for special circumstances such as extremely low birth weight infants.

CALCIUM AND VITAMIN D SUPPLEMENTATION

The use of AEDs may pose an increased risk for osteopenia/osteoporosis and fractures. Enzyme inducing and non-enzyme inducing AEDs can have an adverse effect on bone metabolism, can increase bone turnover, and cause decreases in bone mineral density (BMD).[8,28] Increased vitamin D metabolism and deficiency may be especially problematic with EIAEDs.[28] Based on labs reported in epilepsy studies, what is often seen are normal calcium levels, elevated PTH, and decreased urinary calcium in the presence of vitamin D deficiency, suggesting that calcium is mobilized from bone to maintain serum levels and decreases BMD.[28]

Use of AEDs, especially if enzyme-inducing, may be considered a risk factor for deficiency and consideration should be given to obtaining serum vitamin D hydroxy levels. Additional monitoring is warranted, since vitamin deficiency is not the sole mechanism AEDs can effect BMD. The American Epilepsy Society Task Force on Concerns for Women with Epilepsy has developed a bone health screening and management protocol with monitoring and treatment details, shown by Harden in 2003[28] (Table 4). In this protocol, higher calcium and vitamin D supplement doses are recommended for those found to have osteopenia, while detection of osteoporosis should prompt referral to a specialist for management. Calcium citrate taken between meals will have improved absorption over other forms, and higher doses of vitamin D may be indicated for elderly or homebound individuals. Both calcium carbonate and citrate salt forms will supplement as well as calcium absorbed from dietary sources.[29]

Antiepileptics' effects on vitamin D levels and calcium should be taken into consideration for pregnancy. Increased calcium demands for fetal development can increase risk for maternal bone loss and osteoporosis later in life, and only 6% of childbearing women consume the recommended daily amount of calcium.[29] Studies regarding calcium and vitamin D use in pregnant women on AEDs are limited. Pregnancy or preconception counseling for adult women should involve daily recommended intake of 1000mg/day calcium and at least 600 international units/day vitamin D through diet or supplementation.[29,30] This should also be advised to women on AEDs, with consideration given to higher doses based on labs and clinical status. Routine screening of vitamin D and calcium levels for pregnancy is not necessary[30], although women on AEDs could be

Table 4. Bone Health and Epilepsy Protocol: Screening and Management

All patients ≥ 12 y/o taking AEDs for 2-5 years
↓
DXA Scan

Normal	**Osteopenia**	**Osteoporosis**
Hip and spine T Score > -1 ↓ Calcium 1200mg/day and Vitamin D 400 units/day ↓ Repeat scan in 2-4 years, based on other risk factors (age, gender, family history)	Hip and spine T Score -1 to -2.5 ↓ Obtain labs (serum calcium, PTH, 25(OH)D, TFTs, urine NTX) ↓ Calcium 600mg TID and Vitamin D 800-2000 units/day Improve dietary calcium Weight-bearing exercise Limit soda, caffeine ↓ Repeat DXA in 18 months (try to use same machine) ↓ If stable/improved, continue with above If there is a decline in BMD at hip or spine of > 1%/yr- refer to specialist	Hip and spine T Score > -2.5 ↓ Obtain labs and refer to specialist (rheumatologist or endocrinologist)

(From the American Epilepsy Task Force on Concerns for Women with Epilepsy)
PTH = parathyroid hormone; TFT = thyroid function test; NTX = N-telopeptide; DXA = dual-energy x-ray absorptiometry; 25(OH)D = vitamin D 25 hydroxy
Adapted from Harden CL. Menopause and bone density issues for women with epilepsy. Neurology. 2003;61(6 Suppl 2):S16-22.

considered at risk for vitamin D deficiency and obtaining serum 25-vitamin D hydroxy levels would be indicated. Goal vitamin D levels in pregnancy have not been established; however, levels less than 32 ng/ml may be an indication for higher supplemental dosing. Generally 1000-2000 international units/day is considered safe in pregnancy. Data on higher prenatal doses are lacking, but vitamin D has been considered safe up to 4000 international units/day.[30]

Table 5. Summary of dosing recommendations for folic acid, calcium, and vitamin D

	Folic acid[a,b]	Calcium[b]	Vitamin D[b]
Women of child bearing age	0.4mg/day[9,26]	1000mg/day (>18 y/o) 1300mg/day (<18 y/o)	600 units/day
Preconception for women on carbamazepine, phenytoin, valproic acid, phenobarbital, or primidone	Prenatal vitamin plus Folic acid 1mg TID or Folic acid 2mg BID		
Preconception for women other AEDs	Minimum 0.4mg/day, higher doses may be considered.		

[a]Preconception folic acid should begin 3 months before conception and continue through the first trimester.

[b]Higher doses may be based on serum levels and clinical status. Use of higher doses during pregnancy should be approved in conjunction with OB/GYN.

SUMMARY

Widespread use of AEDs should prompt practitioners to evaluate women for necessary counseling and intervention on issues surrounding contraception and vitamin supplementation. Assuring awareness of the interactions of these medications among clinicians and patients can decrease chance of unplanned pregnancy, birth defects, and loss of seizure control. When using AEDs in women of childbearing age, contraceptive methods and future pregnancy plans should be discussed. Alternative contraception regimens are indicated for concurrent use of interacting AEDs, such as barrier methods, DMPA, IUDs, or COCs with at least 50mcg EE. All women of childbearing age should be advised to take standard recommended doses of 0.4mg/day folic acid, and those planning pregnancy may be considered for higher doses. Since up to half of pregnancies may be unplanned, use of higher folic acid doses could be discussed with patients in the absence of preconception plans. Further studies and reporting are needed in pregnant women on AEDs regarding folic acid, calcium, and vitamin D supplementation to determine optimum dosing. All women on long-term AEDs should be evaluated for osteoporosis with bone density and serum vitamin D level monitoring. Bone health may be improved by intake of 1000mg-1200mg/day calcium through diet or supplementation and at least 600 international units/day vitamin D with weight-bearing exercise. Prenatal care should be coordinated in conjunction with the patient's OB/GYN and neurologist with consideration given to folic acid and vitamin K supplement needs.

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