Pregnancy and epilepsy

SHEIDA SHAAFI .MD

ASSOCIATE PROFESSOR OF NEUROLOGY

TABRIZ UNIVERSITY OF MEDICAL SCIENCE

The Five Principles

1. Choosing the Best ASMs for the Patient's Seizure Type
2. Choosing an ASM or ASMs With the Least Teratogenic and Cognitive Side Effects
3. Dosing to Reduce Complications
4. Promptly Selecting the Best ASM Regimen
5. Supplement All WWE in the Reproductive Age Group With Folic Acid

Choosing the Best ASMs for the Patient's Seizure Type

Broad spectrum ASMs include valproic acid (VPA), lamotrigine, topiramate

Some ASMs such as clobazam and rufinamide are FDA-approved for only certain types of generalized seizures

other ASMs such as brivaracetam, felbamate, zonisamide, and lacosamide are FDA approved to only treat focal seizures

There are, however, narrow spectrum ASMs that can in fact worsen certain types of generalized seizures and are thus used to treat mostly focal seizures(carbamazepine, oxcarbazepine, phenytoin, pregabalin, and gabapentin)

Once the type of seizure is identified the practitioner can then narrow down the ASM list to the ones most suitable for the patient's seizure type.

Choosing an ASM or ASMs with the least teratogenic and cognitive side effects

For WWE in the reproductive age group, narrow the list of ASMs (the lowest rates of MCM)

MCM are structural abnormalities that usually require surgical, medical, and cosmetic services (i.e., cleft lip, cleft palate, malformed limbs, neural tube defects, and cardiac abnormalities)

Since the 1990s birth outcomes of children born to WWE have been closely monitored through different pregnancy registries.

Despite differences in methodology, the registries have generally reported similar findings and have all noted that exposure to VPA poses the greatest risk for MCMs.

They have also shown that both lamotrigine and levetiracetam have a relatively low potential for MCMs.

These findings have led to a marked difference in the way we now prescribe ASMs to WWE in the reproductive age group, with lamotrigine and levetiracetam being the most prescribed ASMs in many countries across the world

Monotherapy vs. Polytherapy

Polytherapy has been shown to increase the risk for major congenital malformation, however recent studies are proving this depends upon specific ASM combinations.

Ultimately, avoiding polytherapy especially in combinations that include VPA is strongly recommended when possible.

Neurocognitive Considerations

There has been growing evidence for the adverse effects of ASMs on **neurocognitive development**.

Children exposed to ASMs (monotherapy lacosamide, valproate, lamotrigine,) and polytherapy had statistically poorer scores for overall development .

Other neurodevelopmental finding showed increased risk of autism spectrum disorders and significantly reduced IQ scores with VPA in comparison to other ASMs

Dosing to Reduce Complications

Dose-dependent risks were observed in the UK & Ireland Epilepsy and Pregnancy Register and the EURAP Registry with **a higher risk of MCM at the higher ASM dosages**

This is particularly true for women taking an ASM such as VPA (>1,000 mg/day in the first trimester,

Higher rates of MCM were observed between low dose and high dose VPA and low dose and high dose carbamazepine, but not markedly different for low and high doses of lamotrigine

More recently, a Cochrane systematic review also supported dose-dependent major malformation risk for carbamazepine (>700 mg/d), lamotrigine (>325 mg/d), phenobarbital (>80 mg/d), and VPA>650 mg/d)

Higher doses of VPA (preconception dose of >900 mg) were also associated with poorer overall developmental scores

Registry	MCM rate following antiepileptic drug exposure				
	Valproate	Carbamazepine	Lamotrigine	Levetiracetam	Topiramate
UK & Ireland Epilepsy and Pregnancy Register (8, 16, 17)	Dose: 0–≤600 mg 24/476 5.0% CI (3.4–7.4%)	Dose: 0–≤500 mg 14/721 1.9% CI (1.2–3.2%)	Dose: 0–≤200 mg 24/1,143 2.1% CI (1.4–3.1%)	2/304 0.7% CI (0.2–2.5%)	3/70 04.8% CI (1.7–13.3%)
	Dose: >600–≤1,000 mg 26/426 6.1% CI (4.2–8.8%)	Dose: >500–≤1,000 mg 20/739 2.7% CI (1.8–4.1%)	Dose: >200–≤400 mg 16/665 2.4% CI (1.5–4.0%)		
	Dose: >1,000 mg 31/297 10.4% CI (7.4–14.4%)	Dose: >1,000 mg 9/170 5.3% CI (2.7–9.5%)	Dose: >400 mg 9/276 3.4% CI (1.9–6.5%)		
EURAP (7, 18)	Dose: ≤650 mg/day 38/600 6.3% CI (4.5–8.6%)	Dose: ≤700 mg/day 58/1,276 4.5% CI (3.5–5.8)	Dose: ≤35 mg/day 46/1,870 2.5% CI (1.8–3.3%)	Dose: 250–4,000 mg/day 17/599 2.8% CI (1.7–4.5%)	Dose: 25–500 mg/day 6/152 3.9% CI (1.5–8.4%)
	Dose: >650–≤1,450 mg/day 75/666 11.3% CI (9.0–13.9%)	Dose: >700 mg/day 49/681 7.2% CI (5.4–9.4%)	Dose: >325 mg/day 28/644 4.3% CI (2.9–6.2%)		
	Dose: >1,450 mg/day 29/115 25.2% CI (17.6–34.2%)				
Australian Pregnancy Register (19)	43/290 14.8% CI (2.11–12.95%)	24/409 5.9% CI (0.8–5.33%)	20/406 4.9% CI (0.66–4.55%)	5/139 3.6% CI (0.37–4.29%)	1/53 1.9% CI (0.09–5.96%)
North American Antiepileptic Drug Pregnancy Registry (20)	30/323 9.3% CI (6.4–13.0%)	31/1,033 3.0% CI (2.1–4.2%)	31/1,562 2.0% CI (1.4–2.8%)	11/450 2.4% CI (1.2–4.3%)	15/359 4.2% CI (2.4–6.8%)

Table adaptation obtained from Elsevier, Kinney and Craig (21).
CI, 95% Confidence interval.

Promptly Selecting the Best ASM Regimen

Changing medications while the patient is pregnant exposes the patient and her fetus to the unknown effectiveness of the new ASM,

thereby, placing the woman at risk of having seizures during pregnancy.

Epileptic seizures were found to be associated with a 1.36-fold increased risk for low birth weight infants, 1.63-fold increased risk for preterm delivery, and 1.37-fold increased risk for small-for-gestational-age

Moreover, the effects of generalized tonic-clonic seizures during pregnancy are particularly worrisome as they can lead to

fetal asphyxia, fetal bradycardia, reduced uterine contractions, direct injury (both to the mother and fetus), and fetal demise.

Supplement All WWE in the Reproductive Age Group With Folic Acid

Folic Acid exposure has been shown to prevent neural tube defects in the general population

Given that ASMs such as VPA can interfere with neural tube development it has become standard of care among epileptologists, to provide relatively high dosing of folic acid in the range of 2–5 mg

Recent literature, however, has shown that folic acid may be beneficial in reducing the risk of autistic traits, enhancing children's IQ, and language development if the mother has taken folic acid for 4 weeks pre-gestation and post-conception

Use of about 4 mg of folic acid in patients who are taking ASMs that impair folic acid absorption (such as phenytoin, carbamazepine, and phenobarbital, as these can cause a deficiency of folic acid by interfering with the way it is absorbed).

Patients taking VPA or who have a history of neural tube defects in their family should also be supplemented with about 4 mg of folic acid.

What is known about the changes in clearance rates of ASMs during pregnancy?

AEDs should be administered at the **lowest effective dose** to control seizures to the optimal level.

It is important to establish the ideal target concentration for each woman prior to entering pregnancy

(an important goal during pregnancy and dramatic pharmacokinetic changes)

Pregnancy is accompanied by many alterations in drug metabolism, including increased hepatic metabolism, renal clearance, and volume of distribution, as well as decreased gastrointestinal absorption and plasma protein binding

As an example, for AEDs that are highly protein bound (eg, phenytoin, phenobarbital, valproate, carbamazepine), the total plasma drug level may decrease with impaired protein binding, but the physiologically important free or unbound drug concentration may not change as much.

Increases in AED clearance

A 2019 report from the International League Against Epilepsy (ILAE) Task Force on Women and Pregnancy concluded that the most pronounced increases in AED clearance (with corresponding decreases in serum levels) during pregnancy are seen with lamotrigine, levetiracetam, and oxcarbazepine

but a clinically important increase in clearance also occurs with phenobarbital, phenytoin, topiramate, and zonisamide

Lamotrigine

A substantial increase in lamotrigine clearance between prepregnancy baseline and the second and third trimesters

Seizure frequency significantly increased when the lamotrigine level decreased to <65 percent of the preconceptional individualized target lamotrigine concentration.

A meta-analysis, with data from six observational studies, suggested that monitoring of lamotrigine levels in pregnancy reduces seizure deterioration .

Levetiracetam

Small studies demonstrate that levetiracetam levels decrease by 40 to 62 percent during the second and third trimesters

Carbamazepine

One exceptional finding in several studies was that the women on carbamazepine had very low rates of worsened seizure control (0 to 15 percent) and **were less likely to have dose adjustments during pregnancy**

Carbamazepine may be a particularly good choice for women with focal-onset seizures when monitoring for AED blood levels during pregnancy is not readily available; additional favorable features of carbamazepine include

its relatively low structural teratogenic risk and **the normal neurocognitive** profiles of children following prenatal exposure

Summary of projected decreases in serum concentrations of individual antiepileptic drugs during pregnancy (if no dose changes are made)

AED	Decrease in serum concentration	Decrease in serum free (unbound) concentration	Recommendations to perform therapeutic drug monitoring, if available
Phenobarbital	Up to 55%	Up to 50%	Yes
Phenytoin	60 to 70%	20 to 40%	Yes, free concentration
Carbamazepine	0 to 12%	None	Optional
Valproate	Up to 23%	None	Optional, free concentration if done
Oxcarbazepine monohydroxy-derivative (MHD)	36 to 62%	N/A	Yes
Lamotrigine	0.77 of population: 69% decrease 0.23 of population: 17% decrease	N/A	Yes
Gabapentin	Insufficient data	N/A	Yes
Topiramate	Up to 30%	N/A	Yes
Levetiracetam	40 to 60%, with maximal decrease reached in first trimester	N/A	Yes
Zonisamide	Up to 35% but little data	N/A	Yes

Changing antiepileptic drugs during pregnancy

As heightened vulnerability to any potential teratogen exists primarily in the

first nine weeks after the last menstrual period, significant exposure has likely already occurred by the time of missed menstruation (4 to 5 weeks) or presentation to prenatal care (8 to 12 weeks).

Therefore, it is usually unwise to alter AEDs during an established pregnancy purely out of a concern for minimization of teratogenic risk.

Furthermore, altering an AED regime often involves the synchronous overlapping of medications, with the potential for the interaction of effects associated with the individual agents described above.

Finally, patients undergoing medication transitions are at increased risk of seizure occurrence

What is known about the risks to children born to women who use antiseizure medications (ASMs) during pregnancy?

VPA exposure should be avoided in women of childbearing potential whenever possible

It is recommended that WWE become pregnant after seizure freedom and withdrawal of ASMs for 6–9 months, mainly because the best predictor of seizure control during pregnancy is the seizure control prior to pregnancy

ASMs that can impair the contraceptive efficacy of hormonal contraceptives by increased clearance of the synthetic steroids include strong enzyme inducers like (CBZ), (PHT), (PB) and (PRM), and mild enzyme inducers like topiramate (TPM), oxcarbazepine (OXC), and felbamate

On the other hand, OCs containing estrogen could decrease the concentrations of some ASMs such as (LTG)

- Generally, polytherapy is associated with a higher teratogenic risk than monotherapy

- VPA has the highest teratogenic risk among all the monotherapies
- Recently, a meta-analysis has also suggested that VPA or TPM exposure in uterus is highly associated with major congenital malformations (MCMs) in infants and children,
- While the odds ratio of MCMs is low in the offspring of women with uterus exposure to LTG or levetiracetam (LEV)
- They should also enquire the patient whether and what OCs she is taking, and then prescribe ASMs without interactions with OCs (such as LEV).
- Barrier method like condom and long acting reversible contraception
- should be recommended if the patient must take enzyme-inducing ASMs or lamotrigine to control seizures.

	MCMs							Combined fetal losses	Prenatal growth retardation	Preterm birth
	Overall	Cardiac disease	Cleftlip/palate	Club foot	Hypospadias	Inguinal hernia	Undescended testes			
LTG	0.96 [0.72, 1.25] 6290	0.55 [0.32, 0.95] 4788	1.21 [0.45, 3.20] 4664	0.70 [0.12, 2.89] 1621	0.66 [0.23, 2.26] 95	0.86 [0.17, 5.92] 81	0.31 [0.05, 1.66] 1660	1.38 [0.70, 2.88] 2540	0.90 [0.56, 1.42] 2882	1.05 [0.70, 1.48] 3015
VPA	2.93 [2.36, 3.69] 4455	1.54 [0.98, 2.37] 3194	3.26 [1.38, 7.57] 2721	3.26 [1.43, 8.25] 802	2.58 [1.24, 5.76] 1437	1.64 [0.39, 10.02] 1845	1.10 [0.33, 3.78] 542	1.83 [1.04, 3.45] 2612	1.28 [0.86, 1.95] 1622	0.96 [0.65, 1.37] 1694
OXC	1.32 [0.72, 2.29] 372	0.69 [0.20, 2.18] 346	3.33 [0.66, 11.80] 304	2.40 [0.24, 13.37] 198	5.19 [0.95, 20.58] 200	1.17 [0.02, 17.89] 189	0.25 [0.00, 5.19] 182	1.66 [0.50, 4.50] 567	0.99 [0.56, 1.76] 1002	0.80 [0.51, 1.26] 1045
TPM	1.90 [1.17, 2.97] 599	0.66 [0.16, 2.11] 429	6.12 [1.89, 19.05] 429	1.77 [0.16, 11.44] 359	3.52 [0.77, 15.72] 429	1.52 [0.13, 14.90] 429	0.14 [0.00, 2.72] 359	23.58 [1.18, 549.60] 2	2.64 [1.41, 4.63] 472	1.38 [0.73, 2.35] 408
LEV	0.72 [0.43, 1.16] 1015	0.25 [0.03, 0.96] 754	0.48 [0.07, 2.18] 872	0.26 [0.00, 3.80] 450	0.29 [0.00, 2.56] 754	1.75 [0.22, 14.87] 1845	2.07 [0.38, 1221] 450	2.47 [0.50, 10.15] 28	1.27 [0.34, 3.54] 81	0.87 [0.31, 2.04] 93
CBZ	1.37 [1.10, 1.71] 8437	0.93 [0.62, 1.43] 1436	1.39 [0.56, 3.15] 5577	1.64 [0.68, 3.62] 99	1.09 [0.53, 2.61] 3540	1.54 [0.40, 8.78] 3307	0.53 [0.14, 1.96] 1386	1.25 [0.73, 2.36] 3911	1.15 [0.77, 1.67] 2897	1.10 [0.77, 1.56] 2141
PHT	1.69 [1.30, 2.17] 2237	0.99 [0.60, 1.57] 1697	3.11 [1.30, 7.72] 1172	2.73 [1.13, 6.18] 932	1.12 [0.51, 2.26] 1350	1.54 [0.38, 9.12] 878	1.27 [0.40, 4.38] 629	1.50 [0.85, 2.91] 618	0.68 [0.37, 1.21] 519	1.03 [0.55, 1.82] 283
PB	1.83 [1.35, 2.47] 1709	1.54 [0.96, 2.57] 1255	5.74 [2.41, 24.08] 894	1.38 [0.51, 3.42] 1057	1.53 [0.60, 3.84] 3824	1.21 [0.26, 7.54] 484	0.94 [0.27, 3.32] 526	0.90 [0.44, 1.93] 407	1.88 [1.07, 3.32] 400	1.59 [0.87, 2.75] 206

Table 5 Recommendations from guidelines on monitoring plasma concentration ASMs during pregnancy

From: Managing reproductive problems in women with epilepsy of childbearing age

Guidelines	Recommendation
AAN/AES 2009 [36]	Monitoring should be considered routinely for LTG (seizure frequency is probably increased when 65% of target level is reached), CBZ, and PHT. Monitoring may be considered routinely for OXC and LVT.
NICE 2012 (update 2016) [38]	Monitoring is not recommended otherwise in routine. Monitoring is recommended if seizures increase or are likely to increase. Monitoring is recommended if dose needs to be adjusted (Lamotrigine and phenytoin are at risk of low serum levels).
ETDP-EFA 2007 [37]	Monitoring of ASM levels is needed throughout pregnancy. ASM levels should be monitored closely in the weeks following delivery since they may increase gradually. LVT, OXC, and LTG showed elevated levels with days of delivery.
RCOG 2016 [35]	Routine monitoring is not recommended although individual circumstances may be taken into account.
SIGN 2015 [34]	Routine monitoring of ASM concentrations is not indicated. Monitoring can be useful in the following circumstances: for adjustment of phenytoin dose, assessment of ASM adherence and suspected ASM toxicity.

How does pregnancy affect seizure frequency and the need for ASMs

When considering pregnancy, ASMs with high fetal teratognicity (such as VPA or TPM) should be replaced with other ASMs like LEV and LTG.

During pregnancy, monitoring the serum concentration of ASMs (especially LTG) is usefult for the control of maternal seizures with a minimum dose of ASM.

At 18–20 weeks of gestation, obstetricians should offer the patient an ultrasound examination to assess the fetal anatomy and detect MCMs.

One milligram of Vitamin K1 should be administered intramuscularly to newborns of women taking enzyme-inducing ASMs (such as CBZ, OXC and TPM), in order to prevent bleeding diseases.

Meador KJ, Cohen MJ, Loring DW, et al. Two-Year-Old Cognitive Outcomes in Children of Pregnant Women With Epilepsy in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study. JAMA Neurology, 2021; DOI: 10.1001/jamaneurol.2021.1583

highlight of AAN Annual Virtual Meeting 2021.

New findings published in JAMA Neurology suggest there is no difference in cognitive outcomes at age 2 among children of healthy women and children of women with epilepsy who took antiseizure medication during pregnancy. The findings are part of the large research project Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD), which is a prospective, long-term study looking at outcomes in pregnant women with epilepsy and their children. The study was funded by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

This study reports findings from 382 children (292 children born to women with epilepsy and 90 born to healthy women) who were assessed for language development at age 2.
Results suggest that children born to healthy women and those born to women with epilepsy do not show significant differences in **language development scores at age 2**.
Most women with epilepsy in the study were taking lamotrigine and/or levetiracetam.

However, the study did find that those children born to mothers with the very highest levels of antiseizure medication in the blood during the third trimester did have somewhat lower scores on tests in the motor and general adaptive domains, which refer to skills related to self-care, such as feeding.

The children in this study will continue to be followed and will participate in additional cognitive tests through age 6. Results so far indicate that **controlling epilepsy with these medications during pregnancy may be safe for babies**.

Fetal anti-convulsant syndrome

Some AEDs are thought to affect a child's development after they are born.

This is called fetal anti-convulsant syndrome (FACS).

The risk of this happening appears to be higher with sodium valproate than with other AEDs.

Problems with the child's development and learning can include: delayed walking and talking, poor speech and language, and problems with memory, attention, lower intelligence and behavior.

Often these effects are not seen until the child starts to get older, for example when they start nursery or school.

Children exposed to sodium valproate in the womb may also be more likely to have an autism spectrum disorder.

Management of epilepsy during preconception, pregnancy, and the postpartum period

Successful management of these pregnancies therefore ideally involves prepregnancy consultation and close collaboration between the obstetric and neurology providers as a multidisciplinary team.

PERINATAL MORBIDITY AND MORTALITY

A growing body of literature indicates that perinatal morbidity and mortality are increased among women with epilepsy compared with the general population complications range from mild to severe and include preeclampsia, preterm labor, bleeding, placental abruption, poor fetal growth, prematurity, fetal death, and maternal mortality

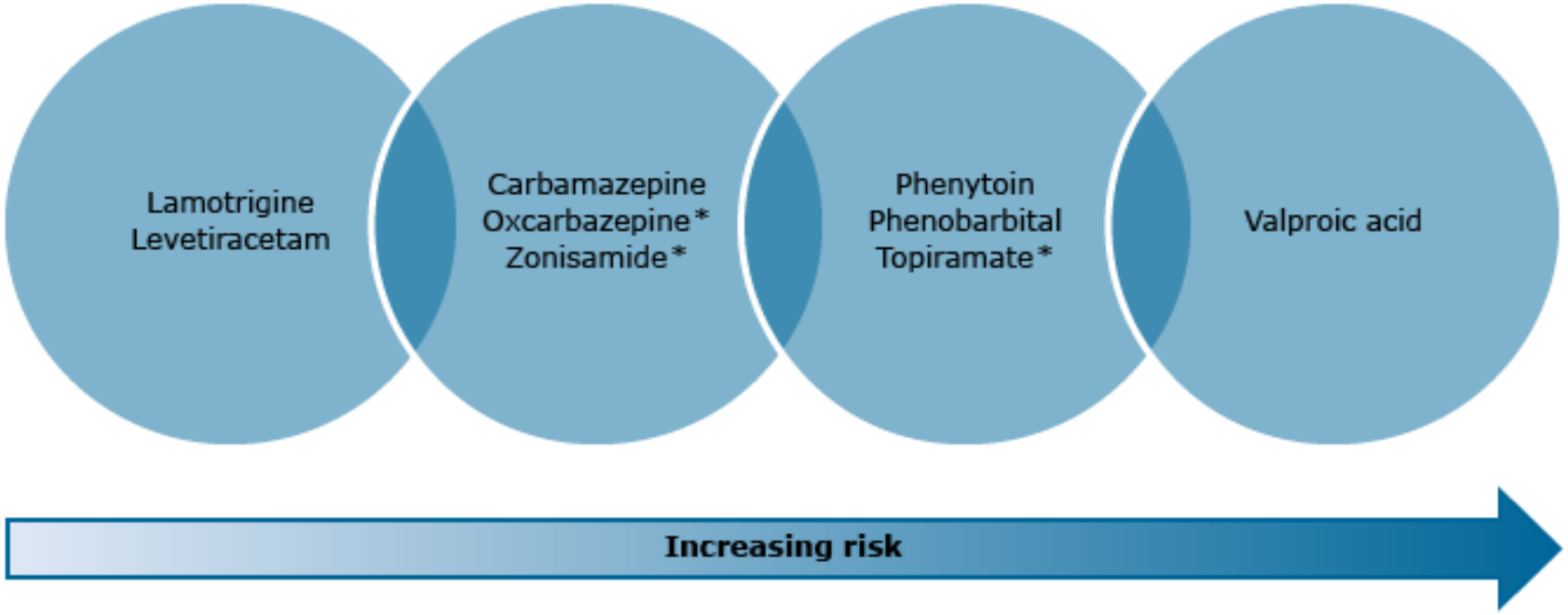
The magnitude of the increase in risk appears to be relatively small for most complications (ie, between 1 and 1.7 times expected rates), with the exception of maternal mortality, which may be as much as 10-fold higher among women with epilepsy during the delivery hospitalization

Choice of antiepileptic drug

For women with epilepsy of childbearing age who are planning pregnancy, **lamotrigine** or **levetiracetam** monotherapy are preferred as first line treatment(low structural and neurodevelopmental teratogenic risk during pregnancy)

However, the clinician should weigh many factors when choosing which AED(s) to prescribe to provide the best balance between maternal seizure control and minimal side effects versus risks to the developing fetus.

Valproate should be avoided in all situations, with the rare exception that it may be used as a last resort


Lamotrigine
Levetiracetam
Carbamazepine
Oxcarbazepine*
Zonisamide*
Phenytoin
Phenobarbital
Topiramate*
Valproic acid
Increasing risk

Approach to a first seizure in pregnancy

Diagnostic considerations for new seizures must include exclusion of possible pregnancy-associated conditions, such as **eclampsia** and **cerebral venous thrombosis**.

Depending on the stage of pregnancy, there may be safety concerns regarding the use of neuroimaging procedures.

Magnetic resonance imaging can be performed at any stage of pregnancy when the information requested .

Gadolinium should generally be avoided in the pregnant patient.

Gadolinium-based contrast agents are present at very low levels in human milk and not absorbed well by the infant gut; no adverse effects have been reported in infants exposed through lactation

Choice of antiepileptic drug treatment

Valproate avoiding

Although lamotrigine is a favorable choice during preconceptional planning, it is not a good choice for initiation during pregnancy; lamotrigine cannot be started quickly due to the higher risk of rash with accelerated titration , and it is difficult to get to a therapeutic concentration due to the enhanced clearance during pregnancy .

Levetiracetam is a medication with a favorable reproductive safety profile, which can be started at a therapeutic dose immediately, and which has a broad spectrum of action across multiple seizure types.

If seizures are focal and begin after the first trimester, carbamazepine is another option given the data supporting normal neurodevelopmental profiles after in utero exposure

Management at delivery

Most women with epilepsy have a normal vaginal delivery

Mode of delivery (by obstetric indications)

However, peripartum is a time of increased seizure risk.

Antiepileptic drug (AED) doses must not be missed during the period of labor.

The Kerala registry of epilepsy and pregnancy reported that seizure relapse was the highest during the three peripartum days, which they counted as the day prior to delivery, day of delivery, and day after delivery

It is therefore essential to maintain the individualized AED target concentration known to protect the woman against seizures during the third trimester and during delivery.

Management at delivery

Consultation with anesthesia should be undertaken early in labor, if not prior to admission for delivery.

We actively encourage our patients with epilepsy to receive neuroaxial analgesia while in labor.

With an appropriately dosed epidural, many women can nap or sleep during the first stage of labor and thereby minimize the potential consequences of sleep deprivation as well as minimize pain-associated stress.

Managing seizures during labor and delivery

Convulsive seizures, if they occur during labor and delivery, should be treated promptly with intravenous (IV) benzodiazepines; **lorazepam** is considered the drug of choice.

To avoid pharmacy-associated delays, it is our practice to have rescue IV lorazepam at the bedside or at least on the delivery floor for all women with epilepsy during labor.

Generally recommend 1 mg IV for nonconvulsive seizures and 2 mg IV for a generalized tonic-clonic convulsion.

The occurrence of a seizure during labor should not alter the intended mode of delivery so long as the seizure can be treated and prophylactic medications administered.

Continuous fetal monitoring should be applied as soon as possible after a seizure is diagnosed.

The fetal heart tracing will be temporarily depressed by a maternal seizure but should return to an appropriate category within five minutes.

Managing seizures during labor and delivery

Given the underlying risk of placental abruption associated with maternal seizure, the progressive deterioration of the fetal heart rate strip or its failure to return to a reassuring status is an indication for an expedited delivery.

Magnesium sulfate is not an appropriate treatment for epileptic seizures.

However, when seizures first present during the third trimester of pregnancy or the early postpartum period, it may be difficult to distinguish eclampsia from a new onset or late relapse of epilepsy.

Immediate consultation with maternal-fetal medical personnel is warranted in this circumstance.

Treatment of eclampsia and evaluation of other etiologies for the seizure is warranted.

The treating team should simultaneously evaluate for a recurrent epileptic seizure and check AED levels while excluding potential precipitants.

Antiepileptic drugs and neonatal sedation

After delivery, phenobarbital, primidone, and benzodiazepines remain in neonatal plasma for several days.

These medications can cause sedation and hyporesponsiveness in the newborn, and evaluation and resuscitation should be undertaken by qualified neonatology personnel

However, AED polytherapy and a high drug burden may be associated with a higher risk for neonatal sedation, decreased responsiveness, and poor feeding, and the newborn may develop features similar to the neonatal abstinence syndrome over the first few days of life

Management in the postpartum period

Postpartum antiepileptic drug tapering

renal and some hepatic enzymatic function (eg, glucuronidation) associated with pregnancy will rapidly resolve over the first two to three weeks postpartum, while other hepatic enzymes (many of the cytochrome P450 enzymes) may take one to two months to return to baseline clearance rates.

It is usual to hold at the delivery dose until postpartum day 3, and then taper over the appropriate interval for the AED.

Management in the postpartum period

●Decrease lamotrigine and levetiracetam over two to three weeks postpartum,

and do the same for other medications that are cleared via hepatic glucuronidation or renal excretion (eg, eslicarbazepine, gabapentin, lacosamide, oxcarbazepine, pregabalin, rufinamide, topiramate, valproic acid, vigabatrin).

●For medications metabolized by the cytochrome P450 enzymes (eg, carbamazepine, clobazam, ethosuximide, felbamate, perampanel, phenobarbital, phenytoin, primidone, tiagabine, zonisamide), tend to taper more slowly, over approximately six weeks

Lamotrigine

Lamotrigine clearance decreases quickly in the first few weeks postpartum, and dose adjustments should be made relatively quickly.

Aim for reaching our target dose at approximately two weeks postpartum.

Breastfeeding

Taking AEDs does not contraindicate breastfeeding

Clinicians should reinforce the benefits.

In agreement with a 2019 report from International League Against Epilepsy (ILAE) Task Force on Women and Pregnancy [2], we encourage women to consider breastfeeding, but with adaptation according to how sensitive their seizures are to sleep deprivation, based upon their history and their epilepsy syndrome.

Many women choose to breastfeed but will introduce the bottle in the hospital.

This allows another adult to give at least one feeding via bottled formula or pumped breastmilk, permitting the mother to obtain at least one four-hour stretch of uninterrupted sleep per 24 hours.

Recommend this and another two hours of sleep through naps to achieve a minimum of six hours of sleep per 24 hours to reduce the risk of seizures

Breastfeeding

All of the AEDs are measurable in breast milk, but levels in breast milk are variable

The reported percentage of maternal plasma levels in breast milk varies from 5 to 10 percent with valproate, to 41 percent with lamotrigine to 90 percent with ethosuximide to 100 percent with levetiracetam .

Summary and recommendations

Epilepsy is not a contraindication to pregnancy

Women of childbearing potential should be counseled regarding the interactions between AEDs and hormonal contraceptive therapy, the potential risks associated with epilepsy and pregnancy, and the importance of folic acid supplementation starting before conception to prevent neural tube defects.

Preconception counseling should include providing options for other forms of effective contraception, especially for patients on an enzyme-inducing AED

For women taking carbamazepine or valproate, or those with a previous pregnancy affected by a neural tube defect or with a neural tube defect affecting either parent, we suggest folic acid 4 mg daily

Some experts advise folic acid 4 mg daily for all women of childbearing potential taking any AED, beginning prior to conception and continuing throughout pregnancy

Recommendations

Valproate should be avoided and only prescribed if no other AED is effective for that particular patient.

Overall, monotherapy is preferred if possible

Increased AED clearance during pregnancy can lead to seizure deterioration (increased frequency or severity) if target blood levels are not maintained.

Monitoring AED levels during pregnancy. Our preferred schedule is to test levels every four weeks, and more often if seizures increase or side effects worsen

Recommendations

With a few exceptions, the approach to the diagnosis and management of a first seizure in pregnancy is the same as in a nonpregnant individual.

Additional diagnostic considerations include pregnancy-associated conditions such as eclampsia and cerebral venous thrombosis.

The choice of AED treatment is complicated by concerns of fetal safety **levetiracetam** has a favorable reproductive safety profile, can be started at a therapeutic dose immediately, and has a broad spectrum of action across multiple seizure types.

If seizures are focal and begin after the first trimester, carbamazepine is another option

Recommendations

The mode of delivery should be dictated by obstetric indications; most women with epilepsy have a normal vaginal delivery. However, peripartum is a time of increased seizure risk.

AED doses must not be missed during the period of labor. Convulsive seizures, if they occur during labor and delivery, should be treated promptly with intravenous benzodiazepines; **lorazepam** is considered the drug of choice

AED therapy is generally not considered a contraindication to breastfeeding

Thank you for your attention
It will be welcome to answer the questions


DELGARM.COM