FOGSI - ICOG

Good Clinical Practice Recommendations

GCPR

Epilepsy

Convenor – Manoj Chellani Co-Convenor – Ranjana Khanna

Mentors – Hrishikesh D Pai, Madhuri Patel, Laxmi Shrikhande

Advisors – Sanjay Gupte, Hema Divakar

National Co-ordinators – CN Purandare, Rishma Dhillon Pai, Nandita Palshetkar, Jaydeep Tank

Co-ordinator – Surekha Tayade

Medical Disorders Committee

FOGSI-ICOG
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Medical Disorders in Pregnancy Committee

Fogsi Good Clinical Practice Recommendations

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INTRODUCTION

The International League Against Epilepsy formulated a modified definition of epilepsy as follows.[1]

Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring >24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome.

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

A seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures. According to the World Health Organization (WHO), 50 million people suffer from epilepsy and among them, 80% reside in developing countries.[2] The prevalence of epilepsy is about 1% in our population.[3] Prevalence is lower in urban (0.6%) compared to rural population (1.9%).[4,5] It is estimated that there are about 2.73 million women with epilepsy (WWE) in India and 52% of them are in the reproductive (15–49 years) age group.[6] The risk of death is increased ten-fold in pregnant WWE.[8]

BACKGROUND

Women experience more social stigma associated with epilepsy than men and have more difficulty with education and employment. They have more difficulty getting married and sustaining successful family life. Reproductive hormones, such as estrogen and progesterone, have an opposing effect on seizure threshold.[7] The anticonvulsant property of progesterone is largely exerted through its metabolite, allopregnanolone, which is a gamma-aminobutyric acid (GABA) receptor-modulating neurosteroid. WWE have an increased risk of infertility, especially if they are on polytherapy. In a study conducted by the Kerala Registry of Epilepsy and Pregnancy (KREP), congenital malformations were detected in 12.5% in WWE.[9] These women constitute a vulnerable group and need special care, especially during pregnancy. The neurologist, gynecologist, radiologist, and pediatrician need to work as a team while managing pregnancy in WWE. It is important to reassure WWE and their relatives that pregnancy is safe and their children are likely to be healthy in more than 90% of instances.[6]

In the absence of national guidelines for the care of WWE during pregnancy, healthcare providers have been following different international recommendations, which are limited in their applicability in the Indian setting. Therefore, there was a need for an expert group to develop evidence-based recommendations suitable for a diverse resource situation as in India.

PURPOSE AND SCOPE OF THE GUIDELINES

The primary purpose of the present guidelines is to improve the quality of care for pregnant WWE. The target audience is obstetricians, physicians, neurologists, epilepsy specialists, general medical practitioners, healthcare managers, public health policy-makers, and those planning research in this topic. Good clinical practice recommendations are formulated considering the multidynamic nature of this country with varied clinical practices and availability of resources. These standards will improve the quality of healthcare services.

STATEMENT OF INTENT

The guidelines are not an endpoint of clinical care but a reference of recommended care. The ultimate decision must be made by the treating physician after discussing all possible and available options with the patient. The guidelines are subject to evolution with advances in scientific knowledge and technology.

METHODS

These guidelines have been formulated by members who are a part of the Medical Disorders in Pregnancy Committee of Obstetric and Gynecological Societies of India (FOGSI) and the All India Congress of Obstetrics and Gynaecology. A panel consisting of Obstetricians of national repute from all the regions of the country and diverse background including professors

and practitioners was constituted. A neurologist was invited as an external expert and was a part of the panel. A guideline template was created that outlined all the relevant topics that needed to be addressed while caring for WWE desirous of pregnancy and those that were already pregnant and those seeking contraception. A special section on antiepileptic drugs (AEDs), a checklist for WWE and for those that took the care of such women, was added as these were unaddressed until now. Every member was provided with a specific part of the draft and the members worked in coordination with each other. Two experts served as moderators and editors. Relevant questions were formulated and distributed among the experts. The literature was reviewed for the past ten years using Pubmed as the primary database along with Cochrane, Embase, Scopus, and Google Scholar. Boolean terms used were epilepsy, pregnancy, seizure, preconception counseling, micronutrients, antenatal care, intrapartum care, postpartum care, breastfeeding, fetal malformations and/or anomalies, AEDs, and contraception. They were used in different combinations to yield maximum targeted results. If relevant articles were outside the search timeline but considered important with reference to the formulated question, they were included. Studies were categorized and rated for quality with regard to study designs and participants, intervention, comparisons, outcomes in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 updated guidelines. A primary draft was prepared and circulated amongst the panel. Weekly online meetings were held and every recommendation was discussed in critical detail. Thereafter, in a face-to-face meeting, the document with various algorithms was discussed and subsequent comments were circulated until unanimous agreement was reached. The draft recommendations were posted online on the FOGSI website for public comments. The final consensus document was presented and was then approved at the FOGSI Managing Committee Meeting.

GRADES OF EVIDENCE FOLLOWED

Grade A	At least one randomized controlled trial (RCT) as a part of a body of the literature of overall good quality and consistency that addresses the specific recommendation.
Grade B	Availability of well-controlled clinical studies but no RCT available.
Grade C	Evidence obtained from the expert committee reports of opinions and clinical experience which indicates the absence of directly applicable study of good quality.
CPP	Evidence not sought. A practice point has been made by guideline developers' group where important issues arose from the discussion of evidence based or clinical consensus recommendation.

LEVELS OF EVIDENCE FOLLOWED

Level I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs) or evidence-based clinical practice guidelines based on the systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from at least one well-designed RCT (e.g. large multisite RCT).
Level III	Evidence obtained from well-designed controlled trials without randomization (i.e. quasi-experimental).
Level IV	Evidence from well-designed case-control or cohort studies.
Level V	Evidence from the systematic reviews of descriptive and qualitative studies (metasynthesis).
Level VI	Evidence from a single descriptive or qualitative study.
Level VII	Evidence from the opinion of authorities and/or reports of expert committees.

1. EFFECT OF PREGNANCY ON EPILEPSY AND EPILEPSY ON PREGNANCY

Pregnancy with epilepsy is a high-risk condition affecting both mother and fetus. Like any other medical disorder, epilepsy has its effects on fetomaternal outcomes and pregnancy also though not profound pregnancy affect the frequency of seizure episodes. Most of the WWE are not fully aware of the facts of the effects of pregnancy and epilepsy on each other. This information is vital for these women before they get pregnant mainly focusing on the need of multidisciplinary care with an obstetrician, neurologist, and fetomaternal medicine expert in an ideal situation.[10]

About 20% of world population with epilepsy live in India. Most of them living in the rural area of the country lack the regularity of treatment due to the feeling of social stigma, cultural beliefs, and the availability of trained professionals. Infectious diseases are one of the most important causes of new-onset epilepsy and status epilepticus in our country.[11]

Here, we review the effect of epilepsy and pregnancy on each other which obstetricians should be aware of helping them for effective and evidence-based counseling for patient awareness and multidisciplinary care.

1.1 Effect of Pregnancy on Epilepsy

Maternal effects are mainly related to the effect on seizures during pregnancy and also the risk of accidental trauma during an episode of seizure.

Most of the women during pregnancy will not have change in the frequency of seizure episodes. A controlled study has concluded that there is no change in the incidence of seizure episode in antenatal women when compared with nonpregnant women studied in the same duration.[12] If the patient is seizure-free 1 year before the pregnancy, then mostly women remains seizure free during pregnancy also.[13]

Women having focal epilepsy are at a higher risk of increasing the frequency of seizure during pregnancy compared to those with generalized epilepsy. Maximum risk reported is with frontal lobe epilepsy. The end of the first trimester and second trimester are the times when the women of focal epilepsy have a higher incidence of the relapse of seizures. Overall, the relapse of seizures is found highest in peripartum period.[14]

Women who have a poor control of seizures prepregnancy and those who are on multiple drug therapy have an increase in the number of seizures during pregnancy.

Noncompliance with medications, intractable vomiting of pregnancy, and incorrect dose adjustment of AED therapy are important factors related to seizure relapse in pregnancy. The fall in plasma drug levels and sleep deprivation are also reported to be contributing factors for seizure relapse.

The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study group studies the treatment changes and control of seizures during pregnancy. They concluded that though WWE remain seizure free during pregnancy, more care is needed to adjust the dose of AEDs during pregnancy.

This care is more needed for women who are on lamotrigine and those who have seizure episode during the first 3 months of pregnancy.[15]

Battino et al. in their review article reported that there is an increased frequency of seizures in labor only 1–2% women have been reported to have an increased number of episodes. Intrapartum.[15] Their findings are similar to that found in the EURAP study. They further suggest that monotherapy at the lowest appropriate dose should be considered while treating WWE during pregnancy to balance the effectiveness of therapy and avoiding adverse effects on fetus.

1.2 Effect of Epilepsy on Pregnancy

1.2.1 Effects on Mother

An epilepsy episode puts an antenatal woman at the risk of adverse events not only for her but for her fetus too. Ideally, women having epilepsy should be counseled preconceptionally about the obstetric complications related to the disease and the need of regular antenatal visits and multidisciplinary care.

Viale et al. in their systematic review studied the effects of epilepsy on pregnancy. Spontaneous abortions, antepartum hemorrhage, postpartum hemorrhage, and hypertensive disorders, preterm labor, and more number of induced labors were the maternal morbidities found in WWE.[16]

The data regarding obstetric morbidities found in WWE are still sparse. Harden et al. in their systematic review concluded that the risk of preterm labor for WWE on AEDs therapy is not more than 1.5 times, a substantial number of WWE who smoke is at an increased risk of premature labor.[17]

Adab et al. reported that there is an estimated 10-fold rise in maternal mortality in WWE compared with women without epilepsy.[17]

A more recent study based on a report from the United Kingdom Confidential Enquiries into Maternal Deaths reported a maternal mortality rate of 1:1000.[18] Almost 60% of these mothers were on lamotrigine therapy. They further stated that this high rate of mortality could be related to the improper dose adjustment of lamotrigine during pregnancy.[8]

1.2.2 Effects on Fetus

The evidence in the literature shows that WWE have a higher incidence of not only the fetal complications, such as congenital malformations, fetal growth, and prematurity, but also issues related to cognition and neurodevelopmental delays detected in the early childhood.

1.2.3 Congenital Malformations

The Cochrane Database of Systematic Review by Jennifer Weston et al. studied the occurrence of congenital malformations during pregnancy. They concluded that there is a higher incidence of fetal malformations found in cases of women taking AEDs therapy and these malformations are peculiar in most of them. There literature search proved that levetiracetam (LEV) and lamotrigine (LTG) therapy was associated with the lowest risk of malformations. Cardiac malformations were more associated with phenobarbital exposure while valproate therapy was associated with neural tube, cardiac, orofacial, craniofacial, and skeletal and limb malformations. The literature is still unclear on the association of dose and the occurrence of malformations.[18]

1.2.4 Fetal Growth Restriction and Prematurity

Women on AED therapy have a higher risk of having fetal growth restriction (FGR). There is a significantly higher occurrence of FGR in women who are on AEDs than in those who are not on therapy.

Hernández-Díaz et al. studied the fetal effects of AEDs and they found that these women are at are at a higher risk of going into preterm labor and having FGR. They reported the prevalence of FGR varied from 7% for LTG to 18% for topiramate.[19,20]

1.2.5 Cognition and Neurodevelopment

There is an evidence that apart from congenital anomalies, neurodevelopmental and cognition issues are found in children born to WWE. Veroniki et al. in their systematic review compared the effect of the maternal exposure of AED therapy on the cognition of children born to them. They stated that women who had five or more bilateral seizures were at a higher risk of having infants developing cognitive delay.

The network meta-analysis (NMA) analyzed 11 cohort studies, 933 children, 18 treatments for effects on cognition and they concluded that valproate therapy was associated with more incidence of cognitive delay and autism. Oxcarbazepine and lamotrigine exposure showed a higher incidence of autism.[21] Cerebral lateralization induced by exposure to AEDs could be the explanation for the cognitive delay found in these infants. Periconceptional folic acid is shown to have normal intelligence quotient (IQ) as found in recent evidence.[22]

1.2.6 Recommendations

i.	Practitioners and healthcare providers should timely counsel WWE, preferably before they get pregnant regarding the need of multidisciplinary fetomaternal monitoring and care so that they make informed choice	(Grade A, Level 1)
ii.	WWE should be counseled that there is no change in the incidence of seizure episode during pregnancy	(Grade A, Level 1)
iii.	Women who have focal epilepsy, poor control of seizures prepregnancy, and those who are on multiple drug therapy should be counseled regarding the high risk of increase in the number of seizures during pregnancy and should be kept under surveillance	(Grade A, Level 1)
iv.	Monotherapy at the lowest appropriate dose should be considered while treating WWE during pregnancy	(Grade A, Level 1)
v.	The dose of AEDs during pregnancy should be revised, especially if there is a seizure episode in the first trimester	(Grade A, Level 1)
vi.	Multidisciplinary management of pregnancy at tertiary care hospitals should be considered as women having epilepsy are at a higher risk of spontaneous abortions, antepartum hemorrhage, postpartum hemorrhage, hypertensive disorders, and preterm labor, and more number of induced labors	(Grade A, Level 2)
vii.	Thorough screening for screening for fetal malformations, FGR should be considered in cases of women taking AEDs therapy during pregnancy due to associated high risk	(Grade A, Level 2)
viii.	Infants and children born to WWE are at a higher risk of developing cognitive delay and should be screened for same	(Grade A, Level 1)

2. PREPREGNANCY COUNSELING

The main aim of preconception counseling is to ensure women embark upon pregnancy with minimum risk, and complete awareness regarding the calculated risk and benefits of proper treatment so that they are able to make informed decisions.

2.1 Information Regarding Expected Pregnancy Complications and Need to Plan Pregnancy

As most pregnancies in WWE are unplanned and any planned interventions need time to implement, counseling must begin as soon as epilepsy is diagnosed and repeated at regular interval.[23]

2.1.2 Recommendations

i.	WWE planning to get pregnant must be provided relevant information about the disease, its effects on pregnancy, and potential challenges. WWE must be provided with a patient information leaflet	(CPP)
ii.	They must be assured that while most pregnancies in WWE are healthy, but they are at a higher risk to develop complications than general population. Proper planning helps improve outcome in WWE	(Grade B, Level 5)
iii.	Good contraceptive advice must be provided, so that pregnancies are planned for optimal outcome. WWE must be counseled regarding higher risk associated with unplanned pregnancies and the benefits of preconception care (*For details on contraception, refer to section on contraception*).	(CPP)
iv.	Women must be informed that, symptom worsening is not expected in two-thirds of women during pregnancy. Information regarding the type of seizure and its effect on baby must be discussed with generalized tonic-clonic seizures more likely to affect the fetus while no effect may be expected from myoclonic, focal, or absence seizures. Even in these cases, injuries from trauma due to fall may affect pregnancy[24]	(Grade C, level 5)
v.	WWE must be informed that if they are seizure free for 9 months to one-year pre conception then they are 80 to 90% likely to remain seizure free during pregnancy	(Grade B, Level 5)

2.2 Genetic Implications

The risk of a child with epilepsy if parents are epileptic is 2.4–4.6%.[25] The risk of epilepsy in the first-degree relatives with genetic generalized epilepsy is six times that of general population. The risk of epilepsy amongst the first-degree relatives with focal epilepsy is increased by 2–3 times that of the general population.[26] The inheritance may be autosomal dominant or recessive with high genetic heterogeneity.[27]

2.2.1 Recommendation

Genetic counseling must be provided to women if any partner has epilepsy. Data regarding actual absolute risk is limited and individualized to the type of epilepsy. Referral to a geneticist must be done for more precise risk estimation if desired by the patient	(CPP)

2.3 Information Regarding Preconception Use of AEDs and Folic Acid

All women must be informed about the need to continue clinically advised antiseizure medications (ASMs) before and during pregnancy and in the postpartum period.

(*For detailed drug information, refer appendix on AEDs in WWE*)

2.3.1 Recommendations

i.	Women must be informed that the risk of congenital malformations in babies born to WWE is greater than the general population	(Grade B, Level 5)
ii.	Folic acid supplementation has beneficial effect in preventing malformations in all women including WWE. The risk of malformations in these women will still remain greater than the general population despite folic acid supplementation	(Grade B, Level 5)
iii.	Women must be informed that folic acid use in WWE is associated with a lower risk of autism and higher intelligence quotient in children, especially in women on ASMs	(Grade B, Level 5)

2.3.2 Dose of Folic Acid

The recommended dose of folic acid varies[28,29] and a higher dose is not harmful (Crawford et al., 1999).[30] Accurate dose that is needed for WWE is not adequately researched.

2.3.3 Recommendation

Folic acid 5 mg/day is recommended during the periconception period in WWE	(CPP)

2.4 Micronutrients and ASM Therapy

Enzyme-inducing ASMs lead to lower plasma vitamin D levels and decrease bone mineral density than nonenzyme-inducing ASMs.[31] This increases the risk of osteoporosis and fractures. However, data regarding findings specifically in pregnant women are lacking and need quality research. In a cross-sectional study of 227 women exposed to ASM were analyzed for serum ASM levels, folate metabolites, riboflavin, pyridoxine, and niacin. High ASM levels were associated with high unmetabolized folate and inactive folate metabolite levels along with the low levels of riboflavin and active pyridoxine with no association with niacin.[32]

2.4.1 Recommendation

WWE must be informed that calcium supplementation must be provided as a part of routine antenatal care and need for altering dose is not yet established	(CPP)

Data regarding other vitamins is scarce during pregnancy and needs research; however, routine supplements with micronutrients in required doses as prescribed in daily requirements may be provided as WWE are likely to develop deficiency, especially when using enzyme inducing AEDs.

3. ANTENATAL MANAGEMENT

The major goal of proper antenatal care for WWE is seizure prevention and reducing risk for mother and fetus. An individualized approach delivered by a team of obstetricians, neurologists, primary care doctors, nurses, and clinical pharmacists with the knowledge of the various aspects of epilepsy in pregnancy is needed to improve outcomes in pregnant patients with epilepsy.[33]

Pregnancy in WWE should be confirmed as early as possible by an accurate documentation of intrauterine location and gestational age should be established before 8 weeks by ultrasonography.[6] The adequate treatment of nausea and vomiting should be done promptly as they interfere with ASM absorption and metabolism.[34] The monotherapy of most appropriate antiseizure drug in the lowest effective dosage should be continued in such a way that seizures are avoided, but with a minimized risk to fetus. Detailed maternal assessment should be done at every visit by thorough history taking about sleep pattern, memory, concentration, tiredness, dizziness, and ASM adherence.

3.1 Recommendations

3.1.1 WWE should be given a written care plan, detailing medications to avoid and what can be done, if women had a seizure or aura.	(CPP)
3.1.2 Seizure provoking stimuli should be avoided, stress should be given on adequate diet and sleep.	(CPP)
3.1.3 Folic acid supplementation in the dose of 5 mg/day should be continued.	(CPP)
3.1.4 A very thorough first trimester screening ultrasound by experienced ultrasonologist to rule out neural tube defects and other anomalies must be done at 12–13.6 weeks.	(CPP)
3.1.5 Maternal serum alpha fetoprotein (AFP) level should be evaluated at 16 weeks and detailed fetal anomaly screening should be performed at 18–22 weeks of gestation to identify all anomalies, especially cardiac, neural tube defect, and facial defects.	(Grade C, Level 3)
3.1.6 Serial growth scan must be done to detect small for gestational age babies.	(Grade B, Level 3)
3.1.7 Cardiotocography as routine antipartum fetal surveillance in WWE taking ASM is not recommended.	(Grade D, Level 4)
3.1.8 Clinicians must be aware of the small but significant increase in obstetric complications such as spontaneous miscarriage, antenatal hemorrhage, hypertensive disorders, fetal growth restriction, premature birth, need for the induction of labor, cesarean section, and postpartum hemorrhage.	(Grade B, Level 2)

3.1.9 Women taking enzyme-inducing ASM, who are at the risk of preterm delivery, can be given antenatal corticosteroid. In these women, the effectiveness of the prevention of respiratory distress syndrome is limited due to increased carbohydrate metabolism. We recommend Betamethasone 12 mg intramuscular 2 doses at the interval of 24 hours, or Dexamethasone 6 mg 4 doses at the interval of 12 hours for prophylaxis against respiratory distress syndrome.	(Grade C, Level 4)
3.1.10 All WWE should be given 2 doses of vitamin K 10 mg intramuscular (IM) at 34 and 36 weeks of pregnancy, unless contraindicated.	(Grade D, Level 4)
3.1.11 One mg of intramuscular vitamin K should be given to all babies born to WWE taking enzyme-inducing ASM to prevent the hemorrhagic disease of the newborn.	(Grade B, Level 3)

3.2 Antiseizure Medication and Monitoring of Drug Levels in Antinatal Period

Pregnancy is associated with hemodilution, altered liver metabolism, and renal clearance. The gastrointestinal absorption of ASM may be erratic and there may be decrease in plasma protein binding. The monitoring of drug levels may be needed for the assessment of ASM adherence and suspected toxicity.

3.2.1 Recommendations

i. Routine monitoring of serum ASM level in pregnancy is not recommended, although individual circumstances may be taken into account. There is no clear evidence to show that therapeutic drug monitoring reduces a risk of seizure compared to monitoring based on clinical features	(Grade B, level 4)
ii. Dose of ASM requires adjustment frequently, especially at 5–6 weeks, again at 10 weeks and every trimester thereafter	(Grade D, level 4)
iii. Some of newer agents, such as lamotigrine, oxcarbamazepine, and levetiracetam, may be more amenable to fluctuation leading to increase in the frequency of seizure, so the drug monitoring of these cases can be done	(Grade C, level 3)

4. INTRAPARTUM MANAGEMENT OF EPILEPSY ANTENATAL PERIOD

4.1 Recommendations

4.1.1 Perinatal care for pregnant WWE should be provided in specialized centers that offer the highest level of perinatal and neurological services	(CPP)
4.1.2 Pregnant women should be counseled that the risk of seizures in labor is low, approximately 1–2%	(Grade A, Level I)
4.1.3 Epilepsy is not an indication for the planned cesarean section or the induction of labor	(Grade A Level I)
4.1.4 There is no indication for an earlier delivery in WWE without obstetric risk factors whose seizures are well controlled	(Grade A, Level I)
4.1.5 WWE have more than a 10-fold increased risk of death, cesarean section, pre-eclampsia, seizures during pre-eclampsia, induced labor, severe postpartum hemorrhage, premature delivery, experience of premature rupture of membranes, and developed chorioamnionitis, and need longer hospital stay	(Grade A, Level II)
4.1.6 All pregnant WWE should be delivered at a tertiary care center	(Grade A, Level I)
4.1.7 Delivery at home is absolutely not recommended	(Grade A, Level I)
4.1.8 To minimize the risk of seizures during labor • Provide adequate analgesia including transcutaneous electrical nerve stimulation (TENS) and epidural • Avoid the use of morphine/pethidine • Hydrate the patient well • Avoid stress • Avoid sleep deprivation • Provide appropriate care in labor.	(Grade A, Level II)
4.1.9 Continue AEDs as per usual dosage during labor. If indicated, parenteral route should be used	(Grade A, Level I)
4.1.10 Long-acting benzodiazepines are preferred if there is a significantly high risk of seizures in intrapartum and postpartum period	(Grade A, Level I)
4.1.11 Continuous fetal monitoring is recommended in women with at a high risk of epilepsy during labor, and following an intrapartum seizure	(Grade A, Level I)

4.2 Management of Seizures during Labor

4.2.1 Recommendations

i. There are chances of maternal and fetal hypoxia and fetal acidosis. Seizures should be swiftly controlled	(CPP)
ii. Follow the principle of ABC • Maintain airway • Oxygen supplementation is advocated • Hydrate well • Give a lateral tilt.	(CPP)
iii. Drug of choice for the control of seizures during labor is benzodiazepines • Intravenous (IV) lorazepam is the first drug of choice: 0.1 mg/kg (usually a 4 mg bolus) with the dose repeated every 10–20 minutes. • In case lorazepam is not available, IV diazepam can be used 5–10 mg in slow IV bolus 2 mg/min. • IV phenytoin is used as the second line when lorazepam/diazepam fail to control seizure; however, close BP monitoring and EEG monitoring are advocated. • Oral medication that can safely be used for controlling seizures is midazolam 10 mg dissolved in 1 mL sterile water.	(Grade A, Level I)
iv. Eclampsia may coexist: This should be diagnosed and treated well in time	(Grade A, Level II)
v. Continuous fetal monitoring is advocated	(CPP)
iv. If the fetal heart shows nonreassuring pattern or does not recover within 5 minutes, delivery should be expedited	(Grade A, Level I)

5. EPILEPSY IN POSTPARTUM PERIOD

5.1 Recommendations

5.1.1 There is a significant risk of seizures in postpartum period[35]	(Grade A, Level I)
The following are contributory factors: • Stress and anxiety • Sleep deprivation • Altered AEDs • Missed AEDs.	
5.1.2 Close monitoring is advocated for the first 24 hours after delivery	(CPP)
5.1.3 Women who suffered seizures during labor should be closely monitored for 72 hours	(Grade A, Level II)
5.1.4 Reassure the mother	(CPP)
5.1.5 Assure adequate hydration	(CPP)
5.1.6 There should be continuous support system in the form of caregiver	(CPP)
5.1.7 Women should ensure that they take their AEDs as prescribed in the postnatal period	(Grade A, Level I)
5.1.8 Watch of daily activities and identifying high-risk situations can reduce the risks	(Grade B, Level II)
5.1.9 In case the doses of AEDs were increased during pregnancy or labor, reducing the same doses should be considered 10 days after delivery to reduce the risk of toxicity	(Grade A, Level I)

6. STATUS EPILEPTICUS IN PREGNANCY AND INTRAPARTUM PERIOD

Status epilepticus is rare in pregnancy and intrapartum period.

6.1 Recommendations

6.1.1 Seizures lasting for more than 5 minutes are likely to progress into status	(Grade A, Level I)
6.1.2 Status epilepticus is defined as a seizure with 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures	(Grade A, Level I)

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6.1.3 Seizures may last up to 30 minutes or a cluster of seizures without recovery	(Grade A, Level I)
6.14 A large data suggested the following reasons contributory to status epilepticus i. Eclampsia ii. Posterior reversible encephalopathy syndrome (PRES) due to various causes other than eclampsia iii. Cortical venous thrombosis (CVT) iv. Subarachnoid hemorrhage (SAH) v. N-methyl-D-aspartate (NMDA) receptor antibody-mediated encephalitis.	(Grade A, Level I)

6.2 Management of Status Epilepticus

6.2.1 Recommendations

i. Involve a multidisciplinary team to diagnose and treat status epilepticus including obstetrician, anesthetist, physician, and intensivist	(CPP)
ii. Follow general principles of ABC. Call for help. Secure airway, initiate oxygenation. Establish IV line.	(CPP)
iii. IV lorazepam is the first drug of choice: 0.1 mg/kg (usually a 4 mg bolus) with the dose repeated every 10–20 minutes	(Grade A, Level I)
iv. In case lorazepam is not available, then IV diazepam can be used 5–10 mg in slow IV bolus 2 mg/min	(Grade A, Level I)
v. If there is no response with 2 doses of benzodiazepines over 20 minutes, then the second-line therapy should be initiated	(Grade A, Level I)
vi. IV levetiracetam 60 mg/kg (up to a maximum of 4,500 mg, patients weighing 75 kg and over) infused over 10 minutes, followed by maintenance dose. Assure normal renal parameters prior to considering this drug. In case of renal impairment, renal doses are preferable	(Grade A, Level I)
vii. Phenytoin in another second-line drug that can be used; however, there is an increased risk of side effects	(Grade A, Level II)
viii. AEDs should be administered concurrently with benzodiazepines	(Grade A, Level I)
ix. The following are drugs that are used concurrently • Fosphenytoin (20 mg/kg) • Phenytoin (20 mg/kg up to 25 to 50 mg/minute) • Levetiracetam (40–60 mg/kg up to a total of 4,500 mg over 15 minutes) • Valproic acid (30 mg/kg at up to 10 mg/kg/minute).	(Grade A, Level I)
x. Suspected eclampsia cases should be treated with Pritchard's regime using magnesium sulfate[36]	(Grade A, Level I)
xi. Guidelines for delivery • Gestational age 24–32 weeks: Close monitoring, steroids, delivery at 34 weeks • Gestational age 34–37 weeks: Close monitoring, steroids, delivery after 48 hours • Gestational age >37 weeks: Deliver.	(Grade A, Level I)
xii. Cesarean section is the mode of choice due to the high chances of fetal hypoxia	(Grade A, Level I)

7. CONTRACEPTION

Every WWE of childbearing potential should be made aware of the importance of effective contraception and the impact of unplanned pregnancy.[37] WWE must be cautioned that enzyme-inducing ASM have bidirectional interaction with hormonal contraception; so, on the one hand, they can lead to decreased effectiveness leading to unplanned pregnancy, and on other hand, they can result in the loss of seizure control and toxicity.[38,39] This is due to pharmacokinetic interaction between enzyme-inducing ASM and hepatic cytochrome P-450 enzyme system and increase the clearance of contraceptive steroid with resultant breakthrough seizures.[40]

Another possible mechanism is by increase in the level of sex hormone-binding globulin, which in turn decrease the level of freely circulating progestin.[41]

7.1 Recommendations

7.1.1 WWE should be offered effective contraception	(CPP)
7.1.2 Nonenzyme-inducing ASM has no effect on hormonal contraception, so every method of contraception may be offered to women	(Grade C, Level 3)
7.1.3 Copper intrauterine devices, levonorgestrel intrauterine system and depomedroxy progesterone injections are reliable contraceptive methods for WWE who are using enzyme-inducing ASM	(Grade B, Level 3)
7.1.4 The levonorgestrel intrauterine system is a very effective form of contraception for WWE as progesterone effect is mediated locally and is not much affected by enzyme-inducing ASM	(Grade B, Level 2)
7.1.5 If women, who are taking enzyme-inducing ASM still choose hormonal contraception, such as oral contraceptive pills, we can increase contraceptive efficacy by increasing the dose of estrogen to 50 micrograms, using extended cycle regimen like 3 packs back-to-back and reducing the pill free internal from 7 to 4 days	(Grade D, Level 3)
7.1.6 The use of higher dose combined oral contraception regimen with enzyme-inducing ASM still carries the risk of contraceptive failure; so, additional backup methods, such as condom and contraceptive gel along with high-dose combined oral contraception, are recommended to improve contraceptive effectiveness	(Grade D, Level 4)
7.1.7 Enzyme induction continues up to 4 weeks after enzyme-inducing ASM has been stopped; so, an alternative backup of contraception must be given during that time	(Grade D, Level 3)
7.1.8 Enzyme-inducing ASM reduces the level of levonorgestrel which make progestin-only pills and implants unsuitable for use in women with enzyme-inducing ASM	(Grade B, Level 2)
7.1.9 Women taking lamotigrine and oral contraceptive pills should be cautioned about the risk of increase in seizure frequency as estrogen containing hormonal contraception increases metabolism of lamotrigine. An increase in lamotrigine dose is required when commencing oral contraceptive pill	(Grade C, Level 2)

Women who are on long-term treatment with carbamazepine, phenytoin, primidone, and valproic acid are at the risk of developing osteoporosis and fracture if the same women is using depotmedroxy progesterone aceatate, osteoporosis risk can be increased further. Strategies must be developed to minimize bone marrow density loss.[42]

7.2 Emergency Contraception

7.2.1 Women using enzyme-inducing ASM, who require emergency contraception should be advised of potential interaction with oral contraceptive pills	(CPP)
7.2.2 They should be offered copper intrauterine device as soon as possible as the most effective method of emergency contraception	(Grade B, Level 3)
7.2.3 If copper intrauterine device is unacceptable or if unsuitable, a double dose (3 mg) of levonorgestrel emergency contraception can be used within 72 hours of unprotected sexual intercourse	(Grade D, Level 3)
7.2.4 Ulipristal acetate for emergency contraception is not recommended in WWE	(Grade C, Level 4)
7.2.5 Additional contraceptive precaution are advised to women and a follow-up pregnancy test is recommended, 21 days after the last unprotected sex	(CPP)

8. BREASTFEEDING

Breastfed children have higher IQ and enhanced verbal abilities. The mother also benefits by a decreased risk of breast and ovarian cancer, cardiovascular disease, and postpartum depression. WWE should be counseled about the relative safety of breastfeeding, even while taking ASM. Women using benzodiazepines and barbiturates should be counseled to monitor their infant for sedation. The ASM concentrations in the blood samples of breastfed infants are substantially lower than the concentration in maternal blood, ensuring the safety of breastfeeding. (NEAD).

8.1 Safety of Breastfeeding

8.1.1 Recommendation

Breastfeeding is considered safe and is recommended for the period of at least 6 months, preferably 12 months	(Grade B,Level 2)

AEDs considered safe: PHT (phenytoin), VPA (valproic acid), and CBZ (carbamazepine).

AEDs considered moderately safe: LTG (lamotrigine), OXC (oxcarbazepine), LEV (levetiracetam), TPM (topiramate), GBP (gabapentin), PGB (pregabaline), VGB (vigabatrin), and TGB (tiagabine).

Caution recommended: PB (phenobarbitone), PRM (primidone), benzodiazepines, ethosuximide, ZSM (zonisamide), and felbamate.

No information available on some newer AEDs: Perampanel, LCM (lacosamide), and eslicarbazepine.

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4): 475-82.
2. World Health Organization. Neurological disorders: public health challenges. 2006. Available from: https://www.who.int/publications/i/item/9789241563369.
3. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia. 1999;40(5):631-6.
4. Leonardi M, Ustun TB. The global burden of epilepsy. Epilepsia. 2002;43(Suppl 6):21-5.
5. Global Campaign against Epilepsy, International Bureau of Epilepsy, International League against Epilepsy (Eds.), 2005. Atlas: epilepsy care in the world. Programme for Neurological Diseases and Neuroscience, Department of Mental Health and Substance Abuse, World Health Organization, Geneva.
6. Thomas SV. Managing epilepsy in pregnancy. Neurol India. 2011;59(1):59-65.
7. Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia. 2012;53(5):e85-8.
8. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia. 2014;55(7):e72-4.
9. Thomas SV, Indrani L, Devi GC, et al. Pregnancy in women with epilepsy: preliminary results of Kerala registry of epilepsy and pregnancy. Neurol India. 2001;49(1):60-6.
10. Dupont S, Vercueil L. Epilepsy and pregnancy: What should the neurologists do? Rev Neurol (Paris). 2021;177(3):168-79.
11. Dhiman V, Menon GR, Kaur S, et al. A Systematic Review and Meta-analysis of Prevalence of Epilepsy, Dementia, Headache, and Parkinson Disease in India. Neurol India. 2021;69(2):294-301.
12. Pennell PB, French JA, May RC P, et al. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. N Engl J Med. 2020;383(26):2547-56.
13. Harden C, Lu C. Epilepsy in Pregnancy. Neurol Clin. 2019;37(1):53-62.
14. Voinescu PE, Ehlert AN, Bay CP, et al. Variations in Seizure Frequency During Pregnancy and Postpartum by Epilepsy Type. Neurology. 2022;98(8):e802-7.
15. Battino D, Tomson T. Management of epilepsy during pregnancy. Drugs. 2007;67(18):2727-46.
16. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet. 2015;386(10006):1845-52.
17. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurosurg Psychiatry. 2004;75(11):1575-83.
18. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;11(11):CD010224.
19. Hernández-Díaz S, McElrath TF, Pennell PB, et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017;82(3):457-65.
20. Veiby G, Daltveit AK, Engelsen BA, et al. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia. 2009;50(9):2130-9.
21. Veroniki AA, Rios P, Cogo E, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017;7(7):e017248.
22. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244-52.
23. Gerard E. Preconception counseling for women with epilepsy. In: Bui E, Klein AM, editors. Women with Epilepsy: A Practical Management Handbook. Cambridge: Cambridge University Press. 2014;141-56.
24. Nucera B, Brigo F, Trinka E, et al. Treatment and care of women with epilepsy before, during, and after pregnancy: a practical guide. Ther Adv Neurol Disord. 2022;15:17562864221101687.
25. Winawer MR, Shinnar S. Genetic Epidemiology of Epilepsy or What Do We Tell Families? Epilepsia. 2005;46(Suppl 10):24-30.
26. Perucca P, Bahlo M, Berkovic SF. The genetics of epilepsy. Annu Rev Genomics Hum Genet. 2020;21:205-30.
27. Guerri G, Castori M, D'Agruma L, et al. Genetic analysis of genes associated with epilepsy. Acta Biomed. 2020;91(13-S):e2020005.

28. Nancy Cheschier; ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin: No. 44, July 2003. Neural tube defects, 2003. Int J Gynaecol Obstet.2003;83(1):123-33.
29. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults: a national clinical guideline. 2018. Available from: https://www.sign.ac.uk/media/1079/sign143_2018.pdf
30. Crawford P, Appleton R, Betts T, et al. Best practice guidelines for the management of women with epilepsy. The Women with Epilepsy Guidelines Development Group. Seizure. 1999;8(4):201-17.
31. Siniscalchi A, Murphy S, Cione E, et al. Antiepileptic Drugs and Bone Health: Current Concepts. Psychopharmacol Bull. 2020;50(2): 36-44.
32. Husebye ESN, Riedel B, Bjørke-Monsen A, et al. Vitamin B status and association with antiseizure medication in pregnant women with epilepsy. Epilepsia. 2021;62(12):2968-80.
33. Borgelt L, Hart F, Bainbridge J. Epilepsy during pregnancy: focus on management strategies. Int J Womens Health. 2016;8:505-17.
34. Patel SI, Pennell PB. Management of epilepsy during pregnancy: an update. Ther Adv Neurol Disord. 2016;9(2):118-29.
35. Chang RSK, Lui KHK, Ip W, et al. Update to the Hong Kong Epilepsy Guideline: evidence-based recommendations for clinical management of women with epilepsy throughout the reproductive cycle. Hong Kong Med J. 2020;26(5):421-31.
36. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol. 1984;148(7):951-63.
37. Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010;3(2):183-92.
38. Schwenkhagen AM, Stodieck SRG. Which contraception for women with epilepsy? Seizure. 2008;17(2):145-50.
39. Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. Contraception. 2011;83(1):16-29.
40. O'Brien ME, Guillebaud J. Contraception for women taking Antiepileptic Drugs. J Fam Plann Reprod Health Care. 2010;36(4):239-42.
41. Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. Seizure. 2015;28:66-70.
42. Berenson AB, Breitkopf CR, Grady JJ, et al. Effects of hormonal contraception on bone mineral density after 24 months of use. Obstet Gynaecol. 2004;103(5 Pt 1):899-906.

ANNEXURES

CHECKLIST FOR PREGNANT WOMEN WITH EPILEPSY

Personal Details

My Complete Name:

My Age:

My Address:

My emergency contact number:

My expected date of delivery is _____

List of allergies that I have:

Any other medical condition that I am having:

My emergency care hospital details: [Name of hospital, Address, Contact Number]: _____

Details about my condition:

1. My seizure type is:
   - Generalized
   - Focal /partial
   - Unknown
2. I had _____ seizure episodes in the last 12 months.
3. Approximate date and time of seizures_____
4. There is aura yes / no
5. Details of what happens during seizure
6. I lose consciousness. / do not lose consciousness during seizure
7. My tongue is injured during seizure yes / no
8. My seizures are triggered by _____
9. My seizures last for _____ hours _____ minutes
10. My care provider's name and contact details:
11. My care provider has been informed about the precautions that need to be exercised and trained in emergency care that needs to be provided in case of a seizure: yes / no

Details of current medications:
[Tick the ones that are ongoing. If you have stopped any medications, check the box saying stopped.]

Name of drug	*Ongoing*	*Stopped*

PERSONAL SAFETY CHECKLIST

1. Ensure that your supply of your medications is accessible all the time. Remember to pack these whenever you will get admitted to your hospital.
2. Carry your medical records and medications with you whenever you travel, visit your clinic, or get admitted.
3. Try not to travel alone. It is safer not to stay in a single room in a hotel to ensure safety in case of an unexpected seizure.
4. Set reminders / alarms for medications to ensure proper dose timing and compliance.
5. Try to take your ASMs as prescribed by your treating neurologist and obstetrician. Avoid missing doses to ensure best pregnancy outcome.
6. Avoid seizure triggers. Try mental relaxation and have adequate sleep. Seek help from your doctors and care providers whenever required.
7. If you have excessive nausea, vomiting, please visit your doctor as you may need to adjust the doses of medications or provided medicines for vomiting as per the case.
8. Eat a healthy diet and light exercise in consultation with your doctors to ensure good pregnancy outcome.
9. Discuss any anxiety that you may have regarding epilepsy with your healthcare provider.
10. If you feel that you may have a seizure, it is advisable to shout and warn your caretakers or healthcare providers so that immediate care is provided.
11. Discuss the problems associated with water delivery (for example, chances of seizure while immersed in water and the logistics needed to provide emergency care) with your healthcare provider and make an informed safe choice.
12. Carry your checklist with you to avoid confusion and proper care.
13. Try to remain calm and relaxed and focus on your pregnancy and baby as you have now made a support team that will help you safely through this pregnancy.

INSTRUCTIONS TO CARE PROVIDERS

- Keep the patient away from danger (fire, water, machinery), tilt her to one side and keep a padded gag or rolled handkerchief between the teeth to prevent tongue bite and a pillow for head protection.
- Educate family and friends.
- Track seizures and medications that your patient is on so that you will be able to provide information to healthcare providers in case of emergency.
- *Think safety*: Seizures are often unpredictable, so preparing safe spaces in the home will reduce the likelihood of injury such as carpet or rugs on floors.
- Encourage the participation of WWE in community so that she does not feel isolated.

APPENDIX ON ANTISEIZURE MEDICATIONS IN PREGNANCY IN WWE (WOMEN WITH EPILEPSY)

Epileptic Seizures in Pregnancy

Most WWE do not have seizures during pregnancy, whereas a third of them may experience an increase in the number of epileptic seizures occurring during this period. At any time during pregnancy, the first-ever epileptic seizure can occur. These can be symptomatic seizures as a result of metabolic disorders, hypotension, eclampsia, and other general conditions such as central nervous system (CNS) infections or arterial/venous strokes.

Planning for Pregnancy in Women with Epilepsy

Recommendations

Information should be provided regarding the teratogenicity of the ASM being prescribed. If the woman plans to get pregnant, it is important to discuss to switch to an ASM with the least teratogenicity	(CPP)
If the woman is on polytherapy, switch to monotherapy with the least teratogenic ASM at the lowest possible effective dose	(CPP)
If the patient needs to be on valproate to achieve seizure control, the high risk of MCMs (major congenital malformations) and the risk of neurodevelopmental adverse effects should also be discussed	(Grade A)
The patient should also be started on folic acid supplementation at a dose of 5 mg/day, even when not planning to get pregnant	(Grade A)

Factors Determining Selection of an Appropriate ASM by Patient (CPP)

- Seizure-control efficacy (randomized data for focal epilepsy suggest no seizure control difference between carbamazepine (CBZ), lamotrigine (LTG), levetiracetam (LEV), zonisamide (ZSM), eslicarbazepine, and lacosamide (LCM), and in generalized and unclassified epilepsies valproate (VPA) is found superior in efficacy to levetiracetam, lamotrigine, and topiramate
- Side effect profile
- Patient-specific characteristics (i.e., comorbid renal disease, reproductive age, pregnancy, and lactating)
- Cost to the patient.

Key Pointers to Remember When Initiating Polytherapy in Uncontrolled Epilepsy (CPP)

- In general, using the ASMs of different mechanisms is ideal for ASM polytherapy.
- Lamotrigine and divalproex has shown to be a beneficial polytherapy, but should be used cautiously due to interaction between the two ASMs.
- There is no evidence that three ASMs has additional benefit over two ASMs.

Choosing an Appropriate Antiseizure Medication in and Around Pregnancy (Tables 1 and 2)

Recommendations

1. Planning for pregnancy

Ideal to plan for pregnancy when stable seizure control is achieved	(CPP)
If already on ASM with high teratogenic risk (VPA, PB, PHT), shift to drugs with lower teratogenicity (LTG, LEV) and attain stable seizure control to plan pregnancy	(Grade A)
Choose the appropriate ASM for the epilepsy syndrome, with the lowest teratogenic risk (LTG, LEV)	(Grade A)
Titrate to the lowest effective dose, establish individualized therapeutic ASM baseline	(CPP)
Prefer monotherapy over polytherapy	(Grade A)
Some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, PB, PHT)	(Grade A)
Folic acid supplementation is recommended to prevent neural tube defects (NTDs)	(Grade A)

2. Management of epilepsy during pregnancy

Continue the same ASM on which seizure control is achieved already	(CPP)
Pregnancy is not the right time to change the drugs in view of teratogenicity as the risk of adverse fetal outcome is more with uncontrolled/new seizure which can precipitate with drug change than with drug teratogenicity per se	(CPP)
Monitor ASMs serum levels, adjust dosage if levels declines or seizure frequency increases	(CPP)
Prenatal ultrasonographic organ screening is recommended at the 19th to 21st gestational week	(CPP)
Cesarean section is indicated when poor seizure control during pregnancy and high risk for seizures during labor could compromise delivery and increase the risk of complications	(CPP)
Search should be made to find the etiology of new-onset seizures (other than eclampsia) with relevant investigations in consultation with neurologist (causes like cerebral venous sinus thrombosis owing to increased thrombotic tendency)	(CPP)

3. Postpartum

Drug monitoring is suggested in the first week postpartum to adjust the ASMs dosage	(CPP)
To allow the possible effect of sleep deprivation during breastfeeding, it might be advisable to maintain the ASM dosage slightly higher than preconceptional dosage	(CPP)
Breastfeeding is highly recommended with the adoption of strategies to lessen sleep deprivation	(Grade A)
Search should be made to find the etiology of new-onset postpartum seizures (other than eclampsia) with relevant investigations in consultation with neurologist (causes like cerebral venous sinus thrombosis owing to increased thrombotic tendency in peripartum period)	(CPP)

Monitoring Serum Levels of AEDs

Recommendations

Several physiologic changes occur during pregnancy, affecting the pharmacokinetics of ASMs. Increased blood volume and cardiac output resulting in modified drug distribution, changes in absorption and bioavailability, altered protein binding, hepatic enzyme induction, and increased renal excretion resulting in decreased ASM level, which may cause breakthrough seizures. The serum levels of LTG, LEV, or OXC (oxcarbazepine) in pregnant women can decrease by up to 30–50% and may contribute to seizure recurrence.

- It is recommended to monitor the serum levels of these drugs before pregnancy and at least once during each trimester of pregnancy (GRADE C)
- Additional indications for AED level monitoring include noncompliance, poor seizure control, and side effects of AEDs (CPP)

Table 1 Drug dosing and titration of antiseizure medications

Antiepileptic Drug	*Starting Total Daily Dose*	*Target Total Daily Dose; Usual Maximal Effective Dose*
Levetiracetam	20 mg/kg/d	60 mg/kg/day
Brivaracetam	1–2 mg/kg/d	Dose adjustment based on response
Phenytoin	5–7 mg/kg/d	6–8 mg/kg/d; up to 10 mg/kg/d
		(may be guided by serum concentration)
Carbamazepine	10–20 mg/kg/d	<35 mg/kg/d
Phenobarbital	1–3 mg/kg/d	3 mg/kg/d; up to 8 mg/kg/d
Oxcarbazepine	8–10 mg/kg/d	30–50 mg/kg/d; usually
		<60 mg/kg/d
Valproate	15 mg/kg/d	30 mg/kg/d; up to 60 mg/kg/d
		with enzyme-inducing AEDs
Clobazam	0.1 mg/kg/d	1.0 mg/kg/d
Topiramate	1–3 mg/kg/d	5–9 mg/kg/d
Lamotrigine	Regimens not containing Carbamazepine, Phenytoin, Phenobarbitone or Valproate	Week 1 & 2: 25 mg OD Week 3 & 4: 50 mg OD Week 5 onwards: increase by 50 mg/day every 1–2 weeks Maintenance dose: 225–375 mg/day in BID dose
	Regimens containing Carbamazepine, Phenytoin, Phenobarbitone without Valproic acid	Week 1 & 2: 50 mg OD
		Week 3 & 4: 100 mg/day in BID dose
		Week 5 onwards: increase by 100 mg/day every 1–2 weeks
		Maintenance dose: 300–500 mg/day in BID dose

Contd...

Antiepileptic Drug	*Starting Total Daily Dose*	*Target Total Daily Dose; Usual Maximal Effective Dose*
	Regimens containing Valproic acid alone or in combination with other antiepileptic drugs that induce Glucuronidation	Week 1 & 2: 25 mg AD (alternate day)
		Week 3 & 4: 25 mg/day
		Week 5: 50 mg OD
		Week 6: 100 mg OD
		Week 7: 150 mg OD
		Maintenance dose: 200–250 mg/day in BID dose

Table 2 Side effects of antiepileptics drugs

Drug	*Side effects*
Phenobarbital	Agranulocytosis, SJS/TEN, hepatic failure, dermatitis/rash, serum sickness
Phenytoin	Agranulocytosis, SJS/TEN, DRESS, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, adenopathy, pseudolymphoma, neuropathy,ataxia, lupus syndrome, coarse facial features, hirsutism
Valproate	Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash,serum sickness, pancreatitis, polycystic ovary syndrome, hypogammaglobulinemia, tremors
Levetiracetam	SJS/TEN, anaphylaxis and angioedema, pancytopenia, behavioral abnormality, psychosis,hypogammaglobulinemia
Brivaracetam	Hypersensitivity reactions including bronchospasm and angioedema,leukopenia, neutropenia, psychosis
Lamotrigine	SJS/TEN, DRESS/multiorgan hypersensitivity, aseptic meningitis, hypogammaglobulinemia, cardiac rhythm and conduction abnormalities
Carbamazepine	Agranulocytosis, aplastic anemia, SJS/TEN, hepatic failure, DRESS,dermatitis/rash, serum sickness, pancreatitis, lupus syndrome, hypogammaglobulinemia, hyponatremia
Oxcarbazepine	SJS/TEN, DRESS/multiorgan hypersensitivity, agranulocytosis, pancytopenia,leukopenia, hyponatremia
Clobazam	Respiratory depression, SJS/TEN, DRESS
Ethosuximide	Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash,serum sickness, drug-induced immune thrombocytopenia
Lacosamide	Prolonged PR interval, atrioventricular block, multiorgan hypersensitivity,neutropenia
Perampanel	Severe neuropsychiatric effects (e.g. hostility, aggression, suicidal tendency)
Topiramate	Acute myopia and glaucoma, kidney stones, oligohidrosis and hyperthermia(which primarily occurs in children), sedation, cognitive slowing

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Disclaimer - These recommendations for “EPILEPSY” have been developed, to be of assistance to obstetricians, gynecologists, consulting physicians and general practitioners by providing guidance and recommendations for managing women with anemia and suffering from hemorrhagic conditions. The recommendations included here shouldn't be viewed as being exclusive of other concepts or as covering all legitimate strategies. The suggestions made here are not meant to dictate how a particular patient should be treated because they neither set a standard of care nor do they guarantee a particular result. To diagnose patients, choose dosages, and provide the best care possible while also taking the necessary safety precautions, clinicians must rely on their own experience and knowledge. The writers or contributors disclaim all responsibility for any harm and/or damage to people or property resulting from the use or operation of any techniques, goods, guidelines, or ideas presented in this content.