Epilepsy in pregnancy

A comprehensive literature review and suggestions for saudi practitioners

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ABSTRACT

في سياق الثقافة المحلية والمفاهيم الخاطئة المتعلقة بمرض الصرع، يحتاج الممارسون السعوديون إلى خطة علاجية واضحة ودقيقة للنساء المصابات بالصرع لتلبية جميع احتياجات المرضى ويضمن تفهم أزواجهن لوضعهن. يجب أن تتضمن خطة العلاج الاختيار الصحيح للعقار المضاد للصرع ومراقبة مستوى العلاج بالدم والاستشارة المنتظمة للمرضى. مرضى الصرع الإناث في عمر الإنجاب، بغض النظر عما إذا كانوا حوامل أم لا، يجب علاجهم عن طريق العقاقير الأكثر أماناً مع مكملات حمض الفوليك إلى جانب المشورة المناسبة قبل الزواج وقبل الحمل. جميع العقاقير المضادة للصرع قد تكون مسببة للتشوهات الخلقية، لذلك، ينبغي أن تكون استراتيجية اختيار العلاج فردية. ومع ذلك، فإن حمض الفالبرويك، الفينيتوين، الفينوباربيتون، و توبيراميت هي الأكثر ضرراً والأقل تفضيلاً للاستخدام. تماما كما هو الحال مع أي مريض مصاب بالصرع، يفضل اختيار العلاج الفردي أكثر من وضع المريض على عقاقير متعددة، ويجب استخدام أقل جرعة ممكنة. خلال فترة الحمل، تحتاج النساء المصابات بالصرع إلى مراقبة مستوى العقار بالدم بشكل شهري وإعادة تعديل الجرعة، إذا لزم الأمر. الولادة الطبيعية المهبلية آمنة في مثل هؤلاء المرضى ومتابعة ما بعد الولادة ضرورية لوجود الحاجة الى تقليل جرعة العلاج أحيانا.

In the context of local culture and misconceptions regarding epilepsy, Saudi practitioners need a careful management plan for women with epilepsy that satisfies all the patients' needs and ensures their spouses' understanding. Such a management strategy needs to incorporate careful selection and monitoring of anti-epileptic drugs and regular counseling of patients. Female epileptic patients in the reproductive age group, no matter whether they are pregnant or not, should be managed by safest drugs from the earliest with folic acid supplementation along with adequate pre-marriage/conception counseling. All antiepileptic drugs are potentially teratogenic. However, valproic acid, phenytoin, phenobarbitone, and topiramate are least favored for use. Monotherapy is preferred over polytherapy, and the least possible dose should be used. During pregnancy, many epileptic women may need monthly drug level monitoring and dose readjustments. Normal vaginal delivery is safe in epileptic women. Post-partum follow-up with anti-epileptic drug titration may be required.

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Epilepsy is one of the most common neurological diseases worldwide.[1] In Saudi Arabia, its prevalence is 6.54/1000 population.[2] Its prevalence in women is 4.75/1000.[2] For a physician who practices in the community or in any specialized epilepsy clinic, dealing with women with epilepsy (WWE) is a common occurrence. Many of these women are in their reproductive years, and some of them may be pregnant and consume anticonvulsant medications.

Epilepsy and pregnancy interact in a complicated way. The physiological changes that occur to maintain homeostasis continue throughout pregnancy and the new hormonal balance has the potential of altering neuronal excitability and the seizure threshold.[3] In addition, it is well known that anticonvulsant/ antiepileptic drugs (AEDs) interact with female sex hormones (endogenous as well as exogenous) by decreasing their levels.[4] Further, these pharmacological agents may also induce major malformations in the fetus.[5] The teratogenic effects of these drugs indeed pose a serious concern for the patients and their healthcare providers. Moreover, the pharmacokinetics of these

drugs keep on changing throughout the pregnancy because of the changes in the water balance of the body.[6]

Although most pregnancies remain uneventful in epileptic patients, some may present devastating complications. In the recent past, there have been some major advances in understanding the complex interactions between epilepsy and pregnancy and their clinical significance. Most of the information is collected from pregnancy registries all over the world. Many such studies are either observational in nature or cohort analyses. Nevertheless, they constitute a very important source of current knowledge about the subject. Clinical practice guidelines for managing WWE were published by the American Academy of Neurology in 2009[7] and by the National Institute of Health and Clinical Excellence (NICE), UK, in 2012.[8] These recommendations are very helpful in making important clinical decisions and counseling the patients.

Epilepsy is a largely misunderstood disease in the general population, and with specific reference to the residents of Saudi Arabia, they still nurture many misconceptions regarding this disease[9] These misconceptions lead to late diagnoses and missed follow-ups, especially in women.

In this review article, we will discuss the current information and literature about some of the common concerns among clinicians who manage epilepsy in pregnant women, which include possible obstetrical complications, teratogenicity and neurocognitive outcomes in the offspring. We will also outline some recommended practice parameters with specific reference to WWE.

Effect of pregnancy on epilepsy. A few prospective cohort studies have been conducted that show that there is no change in seizure frequency during pregnancy in the majority of WWE.[8] However, the seizures may become more frequent in some (15-37% of epileptic women).[10] Not much is known with certainty as to why some women experience increased seizure frequency during pregnancy. However, some factors that include sleep deprivation, altered anti-epileptic drug (AED) pharmacokinetics, or poor adherence to treatment may play a role. It was also found that women with focal onset epilepsy or those who were undergoing polytherapy experienced increased seizure frequency during pregnancy.[10] During and immediately after labor, there is also a relatively increased risk of seizures (post-partum).[11,12]

Women who have catamenial epilepsy (CE) have been shown to have a better seizure control, during pregnancy as compared to those who do not have CE. Hence, information regarding CE should be considered while taking management decisions and counselling the pregnant women.[13]

Effect of epilepsy on pregnancy. Obstetrical complications: Although most WWE have healthy pregnancies, they are still considered to be at an increased risk of suffering from pregnancy-related complications.[8] This risk is higher when WWE are also on AED therapy.[14] A pregnancy registry from India has shown that WWE are more likely to have spontaneous abortions as well as anemia, ovarian cysts, and fibroid uterus.[15] Meta-analyses and population-based data from many other countries show a small but significant risk of caesarian sections, post-partum hemorrhage, and induction of labor with AED exposure.[14,16,17] This risk should also be considered while counselling WWE.[17] For WWE who do not take AED, there is a slight increase in the risk of cesarian delivery only.[16]

Fetal complications (without AED exposure). Focal seizures including unilateral motor or non-motor seizures, or some generalized seizure types like absence, and myoclonic seizures do not have adverse effects on pregnancy or the fetus. However, they may have indirect but serious consequences if the patient sustains trauma because of them.[8]

Women with epilepsy who experience generalized tonic-clonic seizures may be at a relatively higher risk of harming the fetus during a seizure, even though the absolute risk remains very low and the level of risk may depend on seizure frequency.[8] It should be noted that the risk of experiencing major congenital malformations (MCMs) in the general population varies between 1.6% and 3.2%, and WWE who do not receive AEDs show similar MCM rates.[4] Hence, exposure to AED leads to teratogenic effects.

Fetal complications (with AED exposure). Anthropometric changes. Newborn infants of WWE who are exposed to AED in utero may have low birth weight and may also be small in size for their gestational age.[16] Studies conducted in European and North American countries have shown that such infants have higher rates of low birth weight, preterm birth, intrauterine growth retardation, and smaller head circumference at birth.[18,19] These infants also have lower APGAR score at birth.

Teratogenicity (Table 1).[20-25] The AEDs are among those drugs that are used as long-term medications and, unfortunately, also have substantial teratogenic

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Table 1 - Major congenital malformation rates (mentioned between parenthesis) with common AED monotherapies during pregnancy, compared with unexposed pregnancies, from different registries around the world.

Registry / Study	Healthy$^{\sigma}$	WWE$^{\sigma}$	CBZ	LTG	LVT	VPA	TPM
	n (MCM rate in percentage)						
Pregnancy registry of South India / Thomas et al 2017[19]	319 (3.45)	252 (5.56)	389 (5.40)	38 (2.63)	30 (3.33)	268 (8.96)$^{¥}$	-
North American AED pregnancy registry /Hernandez et al 2012[20]	442 (1.1)	-	1033 (3.0)	1562 (2.0)	450 (2.4)	323 (9.3)$^{¥}$	359 (4.2)$^{¥}$
Australian pregnancy registry / Vajda et al 2014[21]	-	153 (3.3)*	346 (5.5)	307 (4.6)	82 (2.4)	253 (13.8)$^{¥}$	42 (2.4)
Medical birth registry of Norway / Veiby et al 2014[22,€]	771,412 (2.9)	3773 (2.8)	685 (2.9)	833 (3.4)	118 (1.7)	333(6.3)$^{¥}$	48 (4.2)
UK epilepsy and pregnancy register / Campbell et al 2014[23,β]	-	-	1718 (2.6)	2198 (2.3)	-	1290 (6.7)	-
EURAP epilepsy and pregnancy registry / Tomson et al 2011[24,β]	-	-	148 (1.3)	836 (1.7)	-	431 (4.2)	-

WWE - Women with Epilepsy, CBZ - Carbamazepine, LTG - Lamotrigine, LVT - Levetiracetam, VPA - Valproic Acid, TPM - Topiramate, $^{\sigma}$Pregnant women who were not exposed to AED (during the first trimester in case of WWE), n - total number of pregnancies and / or fetuses, either exposed or not exposed (healthy and WWE columns) to AED, from which the MCM rate was determined. $^{¥}$Significant values, where RR or OR was calculated between exposed and unexposed groups, *women who were not healthy, because of epilepsy or other diseases that required AED use, but did not use them during the first trimester, $^{€}$odds ratio was calculated instead of RR, ^{β} no unexposed reference group for comparison, the study compares effect of dose among individual AEDs, and the MCM rate shown in the table is with the lowest dose

effects. Apparently, teratogenicity is variable among many different types of AEDs. We will consider the commonly used AEDs followed by some of the newer drugs separately for this purpose.

Carbamazepine (FDA pregnancy category D). Animal studies have shown a consistent risk of teratogenicity, even though its risk level is the lowest among all AEDs. Human studies have mostly been observational and have not been conclusive, with some showing an increased risk while others find that it poses a minimal risk for the MCMs.[26,27] Morrow et al[28] in 2006 found that it exhibits the lowest risk of teratogenicity. However, this has not been shown consistently in later studies (**Table 1**).[20-25] Carbamazepine is still considered as a safer option among the older anti-epileptics, especially when compared with Valproic acid. A very recent network meta-analysis showed an increased risk of overall MCMs with carbamazepine (OR, 1.37; 95% CrI, 1.10–1.71). Some studies have shown that the teratogenic effect of carbamazepine is rather dose-related.[24,25]

Phenytoin (FDA pregnancy category D). The teratogenicity of phenytoin has been well established among clinicians for almost 40 years.[20-22,29] "Fetal hydantoin syndrome", is found in 11% of newborns who are exposed to phenytoin in utero.[30] An additional 30% of such children express some (if not all) of its features.[31] Infants with FHS suffer from intrauterine growth restriction and intellectual disability. They may also have facial dysmorphism, hypertelorism, depressed and broad nasal bridge with upturned nasal tip, prominent epicanthal folds, and wide prominent vermilion of the lips, digital hypoplasia, and irregular ossification of the distal phalanges.[30,31]

Phenobarbitone (FDA pregnancy category D). The rate of MCM induced by PB monotherapy exposure during pregnancy varies between 2.9% and 6.5% in different studies. A recent network meta-analysis showed significantly higher rates of MCM with phenobarbitone with OR, 1.83; 95% CrI, 1.35-2.47, as compared with controls.[32] A total of 60 to 65% of these malformations are of cardiac origin.

Valproate (FDA pregnancy category D). Data from pregnancy registries and prospective studies have revealed a significantly increased risk of MCMs in the neonates born to pregnant women who consumed valproate during the first trimester of pregnancy (**Table 1**).[20-25] The most common types of birth defects reported are as follows: neural tube defects, orofacial clefts, congenital heart defects, hypospadias, and skeletal abnormalities.[33] In different prospective cohort studies from different populations, the prevalence rate of MCMs with valproate monotherapy ranges from 4.4% to 13.8%.[20-25] The UK and Irish Pregnancy Registries recorded 3 times as many MCM cases from valproate exposure as from Lamotrigine (6.7 versus 2.3%).[24] The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group showed that there is an increased risk of MCM or death with valproate (20.3% with valproate as opposed to 10.7% with phenytoin, 8.2% with carbamazepine, and 1% with lamotrigine).[33] This study further elaborated that this effect is dose-dependent. A recent meta-analysis also revealed that valproate exposure in pregnancy was significantly associated with overall major congenital malformations with an OR of 2.93; (95% CrI, 2.36–3.69).[32] Furthermore, polytherapy regimes that include

Table 2 - Approach towards women with epilepsy in child bearing age and pregnancy (summary of suggestions by the authors).

Confirm the diagnosis of epilepsy	Confirm the diagnosis of epilepsy by seizure type and etiology of epilepsy History and examination are of pivotal importance A video taken by family members, by a smart phone or other gadgets, of the ictal events can be crucial and confirmatory in many cases. Interictal Electroencephalogram can be helpful in classification of the epilepsy type (but should always be interpreted in the clinical context). Video EEG capturing the ictal events may be considered a gold standard to diagnose and classify epilepsy, however, this may not be practically feasible in majority of cases, and patients having indications for this modality should be referred to centers that have the facility of epilepsy monitoring unit. Brain imaging, if indicated, is preferably done with a 3 tesla MRI machine.
Counseling	Should be done after confirmation of epilepsy by its etiology. It should be done along with other family members e.g., spouse, parents, siblings etc. Prognosis of epilepsy and possible duration of therapy should be carefully suggested. In case the patient is married or has plans to get married in near future, a planned pregnancy should be advised, and appropriate contraceptive methods should be suggested. Patient and spouse should be informed about the risks of teratogenicity and fetal growth restrictions associated with AED use. Patients should be given time to discuss their own fears and concerns about their diagnosis and its impact on their personal, social and professional life.
Optimal therapy	Optimal therapy is determined by the epilepsy etiology, and various other patient related factors. Valproic acid, phenytoin, phenobarbitone and Topiramate are least favorable Carbamazepine should not be used in idiopathic generalized epilepsy syndromes. Carbamazepine, Levetiracetam and lamotrigine may be preferred as they have lower risk of teratogenicity. Aim to use a single antiepileptic drug in the least possible dose. Serum drug levels whenever available should be monitored, and at least one trough level when the patient is completely seizure free should be obtained. Folic acid supplementation should be given. Patient should be seizure free for at least 9 months before conceiving
During pregnancy	Patient should be monitored by a combined team of gynecologist and neurologist / epileptologist. Drug levels may be monitored, on a monthly basis (particularly in case of lamotrigine). The pre-pregnancy drug level with total seizure control should be aimed for, during pregnancy. Folic acid supplementation should be continued at 4 to 5 mg /day A level II ultrasound at 18 to 20 weeks gestational age should be offered to the patient for a detailed anatomical evaluation of the fetus. WWE taking enzyme inducing AEDs and whose newborns are at risk of intracranial hemorrhage may be given Vitamin K supplementation in the last month of pregnancy. Normal vaginal delivery can be safely attempted with epidural anesthesia, if required, C-section may be considered in patients who are not able to cooperate during delivery process because of heavy sedation.
Post- partum	WWE should be advised to breast feed their newborns, (because of the usual benefits of breast feeding). Infants should be nursed and carried with some precautions (see text) If AED dose was stepped up during pregnancy then it should be stepped down gradually postpartum to avoid toxicity, while monitoring AED levels It is preferable to keep patient on a slightly higher dose that was before pregnancy (with full seizure control), but less than the pregnancy dose, for 1 to 3 months post-partum, to protect patients from effects of sleep deprivation.

valproate have shown a much increased MCM rate as compared with individual AED, which has also been shown with lamotrigine.[32,33] The dose dependent risk of teratogenecity with valproate has been shown in many pregnancy registries. The risk usually increases when the daily dose exceeds 600 mg / day, but the highest risk is when the dose is 1000 mg / day or above.[24,34] However, individual susceptibility is genetically determined, making some individuals highly susceptible even with very low daily dosages.[34]

Lamotrigine (FDA pregnancy category C). Animal studies have shown that lamotrigine is developmentally toxic in doses that are less than those given to humans. Current data on humans suggest that lamotrigine is less teratogenic than most of other commonly used AEDs, including valproic acid or phenytoin.[20-25] The International Lamotrigine Pregnancy Registry update reported a risk of 2.9% with 414 monotherapy exposures. The North American AED Pregnancy

Registry found only an increased risk of orofacial clefts, with no significant risk of MCMs in 684 infants who were exposed in utero to lamotrigine. However, this increased risk of orofacial clefts was not found in the EUROCAT congenital anomaly registers for 40 children who were exposed to lamotrigine monotherapy. Perhaps, as suggested by some authors, there is a dose-dependent relationship between MCM and maternal lamotrigine use, with the risk of MCM being greater with higher lamotrigine doses.[22] In many registries and meta- analyses carried out so far, Lamotrigine appears to be a safer option, and perhaps one of the least hazardous anticonvulsants than other commonly used AEDs, as far as teratogenecity is concerned (**Table 1**).[20-25,32]

Levetiracetam (FDA pregnancy category C). Levetiracetam in animal studies caused developmental toxicity, and teratogenicity. In humans, the North American Epilepsy Registry reported 450 exposures during the first trimester and showed an MCM rate of 2.4%.[21] However, the rate of MCM is much lower in other registries, e.g., in the UK and Ireland pregnancy registry, the rate of MCM was 0.7% (CI 0.19–2.51%). In the light of the most recent evidence, many authors consider levetiracetam as much safer and with no significant teratogenic effects on the human fetus (**Table 1**).[20-25,32]

Topiramate (FDA pregnancy category D). In multiple animal species, topiramate demonstrated developmental toxicity, including teratogenicity, in the absence of maternal toxicity at clinically relevant doses. In humans, Topiramate exposure has been shown to be harmful for the fetus in pregnant women. The data from pregnancy registries indicate that infants exposed to topiramate in utero are at an increased risk for MCM, cleft lip and/or cleft palate (oral clefts), hypospadias, being small in size for gestational age, and increased combined fetal loss. Some studies have shown variable rates of MCM with topiramate that ranged between 2.4% to 4.2%.[20-25] The North American AED pregnancy registry reported on 359 women with first-trimester exposure, with a prevalence of 4.2% versus 1.1% in the unexposed reference group (with 95% CI; 1.4–10.6).[21]

In a recently published systematic review by Veroniki et al,[32] topiramate exposure in utero was associated with high incidence of MCM, having an odds ratio of 1.90 (95% CrI 1.17–2.97)

Clonazepam (FDA pregnancy category D). Clonazepam is a medication that is widely used not only as an antiepileptic drug. Several studies have also revealed that it is not associated with an increased risk of MCMs if it is used as a monotherapy and that it presents no complications from the obstetric perspective.[32] Some studies have shown that the risk will significantly increase to 6% if it is used as polytherapy.[22]

Clobazam (FDA pregnancy category C). Although limited data are available in regard to exposure to clobazam during pregnancy, benzodiazepines, in general, can have sedative effects on newborns. In a recently published study by Thomson et al., the pregnancy registry of South India showed Clobazam use in 9 patients, and MCM occurred in 2 pregnancies (22%), RR, as compared to unexposed healthy pregnancies, was 6.44 (95% CI 1.67–24.94).[20] This increased risk needs to be confirmed in larger cohorts.

Oxcarbazepine (FDA pregnancy category C). Vajda et al[22] reported the risk of MCM to be 5.9% if oxcarbazepine is used as monotherapy during pregnancy. However, the risk will increase to 11.1% if it used as a polytherapy.Veroniki et al[32] in their network meta-analysis found insignificant association with MCMs, OR 1. (CrI 0.72,2.29)[32]

Zonisamide (FDA pregnancy category C). Kondo et al[35] investigated the impact of zonisamide exposure in pregnancy. They prospectively followed 26 pregnant women, of which 22 were on polytherapy and 4 were on monotherapy. No MCMs were detected in the 4 newborns who were exposed to monotherapy. Only 2 offsprings (7.7%) in the polytherapy group had MCMs, with 1 case of anencephaly and 1 with atrial septal defect. However, as the zonisamide blood levels were low in both cases below the therapeutic range, so the results were not conclusive. A Cochrane database systematic review in 2016 concluded that zonisamide was not associated with an increased risk of MCM, however, very few data for this drug is available.[25]

In 2014, Hernández-Díaz et al[36] demonstrated the relationship between the exposure to zonisamide during pregnancy and low birth weight. A total of 98 exposed pregnancies were followed in their study and the prevalence for low birth weight was discovered to be 12.2%.

Lacosamide (FDA pregnancy category C). Over the span of the past few years, limited information has become available on the safety of Lacosamide during pregnancy. In 2011, Hoeltzenbein et al[37] studied 7 pregnant ladies on lacosamide, of which 1 pregnancy was terminated at the gestational age of 20 weeks due to multiple malformations. However, the mother was on 6 antiepileptic drugs, and lacosamide was started after week 15 of gestational age. They also reported 1 case of spontaneous abortion at the gestational age of 6 weeks. In that series, 5 infants were born, 3 of whom had

congenital anomalies. Major anomalies were reported in 1 of the 3 newborns such as atrial septal defect/patent foramen ovale. In addition, the mother was on other 2 antiepileptic medications. Recently, a case series of 3 patients was studied by Lattanzi et al,[38] in which the 3 pregnant mothers were exposed to lacosamide during pregnancy and breastfeeding with no teratogenicity, no major or minor congenital abnormalities. More studies have to be conducted to study the safety of the use of lacosamide during pregnancy.

Brivaracetam (FDA pregnancy category C). A new anti epileptic for add – on therapy in refractory focal onset epilepsy. There are very limited teratogencity data available in humans. In animal models teratogenecity was observed in maternal toxic doses of BRV.[39,40] In humans it should therefore be used during pregnancy if the potential benefits outweigh possible risks.

Perampanel (FDA pregnancy category, not assigned). The data available in human studies is not sufficient. A review of clinical studies identified 25 pregnancies in 22 women. Only 5 of these resulted in normal healthy infants, there were 12 induced abortions, 5 spontaneous abortions, one neonatal death, while 2 subjects were lost to follow. Perampanel also caused prolonged and irregular estrous cycle in rats, thus may affect fertility in humans. Therefore, currently Perampanel is not recommended for young women in child bearing age without contraception.[41]

Eslicarbazepine (FDA pregnancy category, Not assigned). Animal studies have not shown a significantly increased risk of teratogencity. In humans the data available is not sufficient to draw any conclusions. According to a systematic review by Costa et al, total 91 pregnancies have been notified so far, congenital anomalies were found in 5 cases, and 18 cases resulted in abortion, however, the review concluded that the available data is insufficient , and such pregnancies should be monitored and evaluated further.[42]

In summary, valproic acid has consistently shown a significantly higher risk of teratogenicity, whereas phenytoin, phenobarbitone, and topiramate pose an intermediate risk. Carbamazepine and lamotrigine present relatively lower risks of congenital malformations. The use of levetiracetam appears promising. However, bigger studies are required.

Long-term cognitive outcomes in newborns. Data from registries in different populations have shown that many infants born to WWE and exposed to AEDs may have impaired mental and motor abilities. A prospective study from India showed that almost one-third of the infants who were exposed in utero to different AEDs experienced similar problems at 15 months of age. At the age of 6 years, they were re-examined and found to have a significantly lower IQ score as compared with children without prenatal AED exposure or maternal epilepsy that served as age-matched control.[43] Similar observations were found in other registries. In general, monotherapy with valproate is clearly associated with impairment of cognitive development, as well as autism and autism spectrum disorders. In comparison to valproate, monotherapy with carbamazepine, Levetiracetam, lamotrigine or phenytoin seem to have better cognitive and behavioral outcomes. However, these AEDs may have a subtle effect on cognition and behavior, therefore more data is required to label these AEDs as completely safe in this respect.[43] The AED polytherapy can also produce such long-term effects.

Managing epilepsy in pregnant ladies (Table 2). There are many misconceptions regarding epilepsy in countries such as Saudi Arabia, which results not only in a late diagnosis of epilepsy but also missed or irregular follow-ups in epilepsy clinics. In the light of these observations, the following are the recommended treatment strategies when dealing with WWE:

Folic acid supplementation. It is recommended that all epileptic women and girls (with or without treatment with AEDs) should receive a daily supplementation of folic acid in a dose of 4–5mg/day before any possibility of pregnancy.[8] Folic acid supplementation is believed to reduce the risk of MCMs in the offspring of pregnant, epileptic ladies. Although the evidence to support this hypothesis is not strong enough (class III studies), the studies that have been conducted so far do not show any evidence of harm and, apparently, there is no reason to suspect that it is not effective. Therefore, this recommendation is still valid.[44]

Pre-marriage steps. The aim of managing epilepsy in pregnant ladies should be the same as in any other epileptic patient, that is, the achievement of complete freedom from seizures. However, the management should start before conception or even before marriage. All women who are in their reproductive years, even if they are not yet married, should be put on the safest possible AEDs with monotherapy and the least possible dose. It is advisable to inform all such patients of childbearing age who are on any AED about the teratogenicity of these drugs.

After marriage and before conception, WWE along with their spouses should consult a neurologist. If a couple plans to start a family in the near future, they should be evaluated and properly counseled regarding the possibility of experiencing a change in frequency of seizures during pregnancy. They should also be informed about the possibility of their offspring having abnormalities that include anthropometric anomalies as well as teratogenicity, and its likelihood should be re-

endorsed. If an adjustment is required in medications, then the clinician should discuss the relative benefits and risks of adjusting medication with the patient to enable her to make an informed decision.[8]

It is recommended that before conceiving, WWE should have an adequate seizure-free period of at least 9 months with a single anti-epileptic drug in the least possible dose.[16] It is prudent to start folic acid supplementation after marriage or after the first pre-marriage visit, in case it has not been started before. It is better to maintain a preconception drug level with which the patient is seizure-free and aim to maintain this level during pregnancy.[44] This is especially true with lamotrigine, which has shown to have decreased drug levels during pregnancy, which, in turn, is associated with the loss of seizure control.[6] Similarly, monitoring carbamazepine and phenytoin levels should also be considered.[44] There is a level C recommendation for monitoring levetiracetam and oxcarbazepine according to AAN guidelines.[44] The rest of the AEDs, even though there is no conclusive evidence, may also be monitored, if feasible.[44]

Delivery. Taking vitamin K supplementation during the last month of pregnancy before delivery is advisable for pregnant WWE on enzyme-inducing AEDs who face the risk of intracerebral hemorrhage in the newborns.[44] The delivery should be supervised by an expert obstetrician and a neonatologist. In addition, a neurologist should also be involved as a member of the team providing care to the patient. There is an increased risk of seizures during delivery, which can be caused due to multiple reasons such as physical stress, sleep deprivation, hypoglycemia, inappropriate AED dosage, missing doses, and co-medications. The routine AEDs that the woman was taking should also be administered in the labor room. It is better to obtain the AED levels beforehand to ensure that the drugs are in their therapeutic range. Parenteral lorazepam should be made available in the labor room and can be administered intravenously if the patient has a seizure during labor. The selected patients may require caesarian section if they are unable to participate in labor, for example, due to heavy sedation.

The respiratory efforts of the newborn can be sluggish if the mother takes phenobarbital or another sedative AEDs during pregnancy. A neonatologist or pediatrician should be available to resuscitate the infant. Many authorities recommend administering Vitamin K1 injections intramuscularly to the infant if the mother had received enzyme-inducing AEDs during pregnancy to reduce the risk of hemorrhagic complications in the newborn, even though the evidence supporting its usefulness is very limited.[8,44]

Breastfeeding. It has been shown that traces of maternal AEDs can be secreted in breast milk.[15] Therefore, there is a potential risk that breastfeeding might negatively impact children's development. However, a recent prospective study showed no such effect.[33] On the contrary, few pregnancy registries have shown a positive effect, for example, a better cognitive profile of infants who were breastfed versus those who were not while the mothers were on AEDs (that included carbamazepine, lamotrigine, phenytoin, and valproic acid).[33] However, more prospective studies are required to be conducted to evaluate AED exposure in infants who are breastfed.

The expression of AEDs in breast milk decreases if the protein-binding capacity of the drug is more and vice versa. WWE in their post-partum period should be encouraged to breastfeed their newborns before taking their dosage of AEDs to minimize the flow of AEDs into the breast milk.

It is important to get adequate sleep, which might be difficult during the early post-partum period as it is usually frequently disturbed at this time. This can lead to breakthrough seizures. Such mothers can be advised to use expressed milk to feed their babies during the night. Moreover, WWE are advised to be careful and avoid positions that can be harmful to the baby if a seizure occurs while they nurse their babies so that they do not suffocate or drop the baby or fall over.

In conclusions, gender and age should be important considerations when choosing AEDs for epileptic patients. Patients' and spouses' counselling is very important for managing WWE. As most of the women are already diagnosed with epilepsy before they become pregnant, it is prudent to give the safest medications along with folic acid supplementation from the beginning, even before they get married. Monotherapy is preferred with least possible doses. All AEDs are potentially teratogenic, but some of them such as includes carbamazepine, lamotrigine, and levetiracetam seem to have a better teratogenic profile. However, the decision regarding AED choice should be individualized. Normal vaginal delivery is safe with appropriate pain and adequate seizure control. The patients should also be supervised during the postpartum period as they may need titration of AED doses then.

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