Update to the Hong Kong Epilepsy Guideline: evidence-based recommendations for clinical management of women with epilepsy throughout the reproductive cycle

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ABSTRACT

Since the publication of the Hong Kong Epilepsy Guideline in 2009, there has been significant progress in antiepileptic drug development. New antiepileptic drugs have emerged, and data about their uses have been published. Women require special attention in epilepsy care. Drug teratogenicity, pregnancy, breastfeeding, contraception, reproduction technology, menopause, and catamenial epilepsy are major topics. Antiepileptic drugs should be chosen individually for patients who are pregnant or may become pregnant with consideration of their teratogenicity and seizure control properties. Folate is commonly prescribed for women of childbearing age who are taking antiepileptic drugs. Spontaneous vaginal delivery and breastfeeding are not contra-indicated in most cases but need to be considered individually based on the patient's medical condition and wishes. Serum drug level monitoring of certain antiepileptic drugs during pregnancy and puerperium can guide dosage adjustment. For catamenial epilepsy, intermittent benzodiazepines such as clobazam during the susceptible phase of the menstrual cycle could be a treatment option.

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Introduction

Women need special attention in epilepsy care. They face various challenges related to their reproductive cycles, including pregnancy, breastfeeding, contraception, menopause, and catamenial epilepsy. Antiepileptic drug (AED) options have increased exponentially in recent decades. New data on epilepsy management have emerged since the 2009 publication of the Hong Kong Epilepsy Guideline by the Hong Kong Epilepsy Society.[1] This article aims to update the Society's guideline with a focus on epilepsy management in women. This project

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Preconception counselling and teratogenicity of antiepileptic drugs

Women with epilepsy, preferably with their partner or parents if appropriate, should receive counselling on contraception, conception, pregnancy, breastfeeding, and childcare. Preconception counselling is especially important for women who

香港腦癇指引更新：生殖週期中對腦癇婦女進行臨床管理的循證醫學建議

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自2009年發佈香港腦癇指引以來，抗腦癇藥的開發取得重大進展。新的抗腦癇藥及其用途的數據已被發表。婦女在腦癇治療中需要特別留意。藥物致畸性、懷孕、母乳喂養、避孕、生殖技術、更年期和月經期腦癇是重要主題。考慮到其致畸性和腦癇發作控制特性，應為懷孕或可能懷孕的患者個別選擇抗腦癇藥。葉酸通常用於服用抗腦癇藥的育齡婦女。大多數情況下，自發陰道分娩和母乳喂養不是禁忌的，但須根據患者的醫療狀況和意願作個別考慮。在妊娠和產褥期監測某些抗腦癇藥的血清藥物水平可以指引劑量調整。對於月經性腦癇，在月經週期的敏感階段間歇使用苯二氮卓類藥物（如氯巴沙姆）可作其中一種治療選擇。

will become pregnant, as it may help to ensure good maternal and fetal outcomes.[2] They should be reassured that most women with epilepsy have uneventful pregnancies and deliveries.[2]

The risk of epilepsy in the offspring of women with epilepsy is highly dependent on the parents' epilepsy syndrome status.[3] In general, the risk is slightly higher compared with that of the background population. In a large population-based study, the overall cumulative risk of epilepsy up to age 40 in individuals with epileptic parents was 4.5%, which is about 3-fold higher than that of the general population.[4] Referral to appropriate specialists such as geneticists is appropriate if genetic counselling is indicated.

Animal studies have shown that AEDs can decrease the level of serum folate, increasing the risk of fetal neural tube defects.[5] Neonatal malformations have also been associated with low maternal serum folate levels in humans.[6] All women with epilepsy of childbearing age may be offered folate supplements while on AEDs.[7,8] Although there is no definite consensus about folate dosage, it is reasonable to prescribe oral folate 5 mg daily to women with childbearing potential.[1,2,9]

Many AEDs have the ability to cross the placenta.[7] Data have emerged on the potential risks of in-utero AED exposure to offspring. The risk of major congenital malformations (MCMs) such as hypospadias, congenital heart defects, club foot, cleft lip or palate, and spina bifida in children born to women with epilepsy treated with AEDs during pregnancy is 2 to 3 times higher than the 2% to 5% occurrence rate in the general population.[10,11] Polytherapy probably has a higher risk of MCMs and future cognitive adverse drug effects compared with monotherapy.[12-14] The risk of MCMs may increase

with higher dosages of AEDs.[12] Antenatal screening including fetal ultrasound scan can help to detect major fetal malformations.[2] However, prenatal screening has limitations in terms of malformation detection and cannot provide information about neurodevelopmental complications.[15]

The North American Antiepileptic Drug Pregnancy Registry (NAAPR) reported that phenobarbital monotherapy was associated with an increased MCM rate of 6.5% (95% confidence interval [CI], 2.1%-14.5%) compared with the background rate of 1.6%.[16] The same registry later reported that the MCM risk associated with phenobarbital was 5.5% in a larger group of 199 pregnancies.[17] The teratogenic effects of phenobarbital are probably related to dosage. Data from the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) showed that phenobarbital had an MCM risk of 5.4% (95% CI, 2.51%-10.04%) in the offspring of women taking daily doses <150 mg. The risk increased to 13.7% (95% CI, 5.70%-26.26%) at daily doses of 150 mg per day or above. Phenobarbital may also have deleterious effects on the cognition of offspring.[12,18]

A meta-analysis found that phenytoin had an MCM rate of 7.4% (95% CI, 3.60%-11.11%).[14] The EURAP reported that the MCM rate associated with phenytoin was approximately 6.4% (95% CI, 2.8%-12.2%).[19] The NAAPR reported that phenytoin was associated with a 2.9% risk of MCMs (compared with a background rate of 1.1%).[17] The UK and Ireland Epilepsy and Pregnancy Register reported that the risk of MCMs associated with phenytoin was 3.7%.[20-22] There is also evidence showing that in-utero phenytoin exposure is associated with an increased risk of impaired cognition.[23-25]

Valproate use during pregnancy may be associated with MCMs and long-term negative effects on the cognitive and neurological functions of offspring. Neural tube defects, facial clefts, and hypospadias may be related to in-utero valproate exposure.[13,26-29] A meta-analysis showed that the overall risk of MCMs associated with in-utero exposure to valproate was 10.73% (95% CI, 8.16%-13.29%).[14] The European Surveillance of Congenital Anomalies study found that valproate monotherapy was associated with significantly increased risks of six specific malformations, with the following odds ratios (ORs): spina bifida, 12.7-fold increase (95% CI, 7.7-20.7); atrial septal defect, 2.5-fold (1.4-4.4); cleft palate, 5.2-fold (2.8-9.9); hypospadias, 4.8-fold (2.9-8.1); polydactyly, 2.2-fold (1.0-4.5); and craniosynostosis, 6.8-fold (1.8-18.8).[30] Adverse effects in terms of mental and motor development have been shown to be associated with in-utero valproate exposure in children.[31-35] In 2011, the US Food and Drug Administration (FDA) issued a warning about valproate use during pregnancy because interim results from the NEAD

(Neurodevelopmental Effects of Antiepileptic Drugs) study and other epidemiological studies showed lower cognitive function in children with in-utero valproate exposure.[31,36,37] The NEAD study was a prospective multicentre cohort study conducted in the US and UK. Interim cognitive assessment at age 3 years showed that children exposed to valproate had intelligence quotient (IQ) scores 9 points lower than those exposed to lamotrigine (95% CI, 3.1-14.6; P=0.009), 7 points lower than those exposed to phenytoin (95% CI, 0.2-14.0; P=0.04), and 6 points lower than those exposed to carbamazepine (95% CI, 0.6-12.0; P=0.04). The association between valproate use and detrimental effects on IQ was dose-dependent.[31] When 244 newborn children subsequently completed 6 years of follow-up, mean IQ at age 6 years was lower in children exposed to valproate (97; 95% CI, 94-101) than to carbamazepine (105; 95% CI, 102-108; P=0.0015), lamotrigine (108; 95% CI, 105-110; P=0.0003), or phenytoin (108; 95% CI, 104-112; P=0.0006).[32] Children exposed to valproate were inferior in terms of verbal and memory abilities to those exposed to the other AEDs and in terms of non-verbal and executive functions to those exposed to lamotrigine. High doses of valproate were negatively associated with IQ, verbal ability, non-verbal ability, memory, and executive function.[32] Valproate use during pregnancy may also increase the risk of childhood autism in offspring (adjusted hazard ratio: 2.9; 95% CI, 1.4-6.0).[38,39] In 2013, the FDA strengthened its warning regarding valproate use: it suggested that valproate should only be used in epileptic pregnant women if other medications are ineffective or unacceptable, and it is contra-indicated for migraines during pregnancy. In women with epilepsy who are currently not pregnant but have the potential to become pregnant, valproate should not be considered as the first-line treatment, especially for focal epilepsies, unless there is no other alternative. For cases in which valproate is considered as an appropriate option, like certain idiopathic generalised epilepsies, the dose should be maintained at the lowest effective dose, preferably not exceeding 500 to 800 mg per day.[15] In special circumstances, the use of valproate as initial treatment may be justifiable. For example, it could be used in epilepsies with high likelihood of remission and drug withdrawal before puberty or in patients with severe disabilities that make future pregnancy extremely unlikely.[15] The American Academy of Neurology has recommended that valproate be avoided during the first trimester of pregnancy if possible.[40] However, the use of valproate in women with epilepsy should be individualised with consideration of the dosage administered, seizure control, and potential effects on offspring. In certain cases, especially those of specific epilepsy syndromes such as juvenile myoclonic epilepsy and juvenile absence epilepsy, valproate may be the most suitable choice after balancing its seizure control properties with the potential adverse effects on both the patient and her offspring. Valproate may also be used when clear communication with the patient about the risk-benefit ratio has been undertaken.

Although the number of women with childbearing potential who take valproate is decreasing, there are persistent concerns about inadequate information provided to valproate users about its possible adverse effects on their offspring. Authorities from various countries or regions, such as the UK and the European Union, have adopted specific risk minimisation measures surrounding valproate usage among women with epilepsy. Examples include the provision of information leaflets highlighting the potential teratogenic and neurodevelopmental impacts of valproate exposure in utero, pregnancy tests before valproate prescription, a risk acknowledgement form filled upon valproate initiation and renewed annually by healthcare professionals, and alert cards provided to women with epilepsy with childbearing potential. These could serve as references to healthcare providers in different clinical settings. Direct adoption of these measures may not be feasible in some local situations. Certain practices may be advisable to enhance communication between prescribers and potential childbearing female valproate users. The indications and potential adverse effects of valproate could be communicated to patients in different formats, such as on paper or electronically. The plan of valproate therapy should be reviewed with women with epilepsy with pregnancy potential when clinically indicated, but not necessarily on a yearly basis. Other medical professionals (eg, nurses or pharmacists) could take a role in AED counselling, including advising patients regarding their potential adverse effects. Materials could be provided to patients regarding the drugs' potential implications on pregnancy and fetal outcomes. These could be in the form of leaflets, warning messages, or QR codes on drug packaging. Good documentation of the communication between the clinician and patient, preferably including the family, cannot be overemphasised.

The NAAPR reported that carbamazepine monotherapy during pregnancy had a 2.9% overall risk of MCMs.[17] The European Surveillance of Congenital Anomalies Database reported that the OR of spina bifida related to carbamazepine monotherapy was 2.6 versus no AEDs.[41] The EURAP has also demonstrated a dose-dependent effect of carbamazepine. Carbamazepine doses of >400 mg per day were associated with a significantly higher risk of MCMs (5.3% for ≥400 to <1000 mg; 8.7% for ≥1000 mg) [Table 1[17,19,21,42,43]].

A 2008 meta-analysis showed that lamotrigine

TABLE 1. Risk of major congenital malformations in offspring of women on various monotherapies of antiepileptic drugs. Because the data are not from single studies, direct comparison is inappropriate

Monotherapy	Rate of MCMs (95% confidence interval)
Carbamazepine	
<400 mg	3.4% (1.11%-7.71%)*
≥400 to <1000 mg	5.3% (4.07%-6.89%)*
≥1000 mg	8.7% (5.24%-13.39%)*
Lamotrigine	
<300 mg	2.0% (1.19%-3.24%)*
≥300 mg	4.5% (2.77%-6.87%)*
Phenobarbital	
<150 mg	5.4% (2.51%-10.04%)*
≥150 mg	13.7% (5.70%-26.26%)*
Valproate	
<700 mg	5.6% (3.60%-8.17%)*
≥700 to <1500 mg	10.4% (7.83%-13.50%)*
≥1500 mg	24.2% (16.19%-33.89%)*
Levetiracetam	0.70% (0.19%-2.51%)[21]
Oxcarbazepine	2.2% (0.6%-5.5%)[17]
Phenytoin	6.4% (2.8%-12.2%)[19]
Pregabalin	5.9%[43]
Topiramate	4.2% (2.4%-6.8%)[19]

Abbreviation: MCM = major congenital malformation
* MCM(s) in offspring detected up to age 1 year[42]

monotherapy had an MCM risk of 2.91% (95% CI, 2.00%-3.82%).[14] The NAAPR has indicated that lamotrigine monotherapy carried a 1.9% risk of MCMs.[44] The EURAP pregnancy registry data show a relatively low risk of malformations when using lamotrigine monotherapy at doses <300 mg per day as compared with other AEDs (Table 1).[42] When used as polytherapy, the combination of lamotrigine and valproate may have a relatively higher risk of MCMs (9.1%; OR=5.0; 95% CI, 1.5%-14%) compared with combinations of lamotrigine and other AEDs (2.9%; OR=1.5; 95% CI, 0.7%-3.0%).[44]

The UK and Ireland Epilepsy and Pregnancy Register reported that levetiracetam monotherapy has a 0.70% risk of MCMs (95% CI, 0.1%-2.51%).[21] The MCM risk of levetiracetam as polytherapy was relatively higher at 6.47% (95% CI, 4.31%-9.60%). The MCM rates of polytherapy including levetiracetam varied with different regimens: the combination of levetiracetam and lamotrigine had a risk of 1.77% (95% CI, 0.49%-6.22%) compared with 6.90% (95% CI, 1.91%-21.96%) for the combination of levetiracetam and valproate and 9.38% (95% CI, 4.37%-18.98%) for the combination of levetiracetam and carbamazepine.

The FDA issued a warning regarding an increased risk of oral cleft in children born to mothers taking topiramate based on data from the NAAPR and the UK Epilepsy and Pregnancy Register. The UK registry reported the risk of oral cleft as 29 per 1000 (95% CI, 5-91 per 1000), which is more than 10 times the background risk.[22] The NAAPR reported that the risk of cleft lip associated with topiramate monotherapy during pregnancy was 14 per 1000 (95% CI, 5.1-31 per 1000).[17] The overall MCM rate of topiramate monotherapy has been reported to be 4.2% (95% CI, 2.4%-6.8%).

Pregabalin use in human pregnancy is relatively less studied. As pregabalin is also used for controlling neuralgic pain, clinical studies on pregabalin may involve confounding factors, such as concomitant medications and co-morbidities, which may be different from those of patients with epilepsy only. This may cause confounding factors in clinical studies, as the concomitant medications and disease spectrum may be different from those of patients with epilepsy only. A multicentre study found that the risk of MCMs associated with pregabalin use in the first trimester of pregnancy was 6.0%, compared with an unexposed risk of 2.1% (OR=3.0; 95% CI, 1.2%-7.9%).[45] However, another larger study did not find any significant association between pregabalin use in the first trimester and MCMs. The exposed risk was 5.9%, compared with an unexposed risk of 3.3% (OR=1.78; 95% CI, 1.26%-2.58%) and the adjusted OR was 1.16 (95% CI, 0.81-1.67) according to that study.[43]

Oxcarbazepine is similar to carbamazepine in terms of chemical structure. The NAAPR reported that oxcarbazepine use in pregnancy was associated with a 2.2% risk of MCMs (95% CI, 0.6%-5.5%).[17] The EURAP registry data show a 3.0% MCM risk associated with in-utero oxcarbazepine exposure (95% CI, 1.4%-5.4%).[19]

Pregnancy

Most women with epilepsy have uneventful pregnancies.[2] However, they should be informed about their risks of pregnancy complications. For example, the risks of such complications as needing Caesarean section, spontaneous abortion, pre-eclampsia or pregnancy-induced hypertension, pregnancy-related bleeding complications, fetal growth restriction, and premature uterine contractions, labour, and delivery may be higher than those of women without epilepsy, especially if they are on AEDs.[9,46-48] Seizure freedom for 9 months to 1 year prior to pregnancy is associated with a high likelihood of seizure freedom during pregnancy.[2,9,49-51] Neither increased seizure frequency nor status epilepticus has been substantially associated with pregnancy.[9] There is no evidence that focal seizures with or without impairment of consciousness,

absence, or myoclonic seizures affect pregnancy or the developing fetus adversely unless a fall causes injury or other serious complications. Generalised tonic-clonic seizures may carry a relatively higher risk to the fetus, although their absolute risk level remains very low, and their risk may depend on seizure frequency.[52] The majority of women with epilepsy experience no change in seizure frequency during pregnancy, whereas a minority of them experience either an increase or a decrease in attack frequency.[14,53] The increase in seizure frequency may be caused by a pregnancy-induced drop in AED concentration, sleep deprivation, or lack of drug adherence. Women who contemplate going without AEDs during pregnancy should undergo discussions about the potential risk of inadvertent status epilepticus or sudden unexpected death in epilepsy.[9,52] A balanced discussion may be held with the patient to facilitate informed decision making and provide access to various options. Early and serial fetal ultrasound scans should be offered to pregnant women who are taking AEDs to screen for fetal structural anomalies.[2,54] Additional screening or diagnostic tests, such as maternal serum tests and fetal echocardiography, should proceed according to clinical indications.[2,55] Pregnancy in women with epilepsy optimally involves collaborative, multidisciplinary planning and management. The multidisciplinary team should involve specialists, such as obstetricians and neurologists, who have experience providing care for pregnant women with epilepsy.[56] Monitoring of AED levels during pregnancy may help to guide dosage adjustment. For example, both total and free clearance of lamotrigine may increase substantially during pregnancy, with a peak in the third trimester.[57,58] A decreased lamotrigine level could result in increased seizure frequency. Pregnancy may also affect serum levels of carbamazepine, phenytoin, levetiracetam, and oxcarbazepine to various extents.[7,59-61] Serum level monitoring may be helpful to inform dosage adjustment during pregnancy. In pregnant women presenting with seizures in the second half of pregnancy that cannot be clearly attributed to epilepsy alone, consideration is usually given to pre-eclampsia, in which case definitive diagnosis should be sought by further assessment.[2]

Fetal complications may occur at slightly higher frequencies in pregnancies of women with epilepsy. A systematic review and meta-analysis that included over 2.8 million pregnancies found that spontaneous miscarriage (OR=1.54; 95% CI, 1.02-2.32), preterm birth before 37 weeks of gestation (OR=1.16; 95% CI, 1.01-1.34), and fetal growth restriction (OR=1.26; 95% CI, 1.20-1.33) were more common in women with epilepsy.[48] However, the risks of early preterm birth before 34 weeks, gestational diabetes, fetal death or stillbirth, perinatal death, or admission to neonatal intensive care unit did not differ between women with and without epilepsy. In another large US cohort study, the risks of preterm labour (OR=1.54; 95% CI, 1.50-1.57) and stillbirth (adjusted OR=1.27; 95% CI, 1.17-1.38) were also higher in pregnancies of women with epilepsy.[47] A 1-minute Apgar score of <7 in the neonate may be associated with maternal AED use.[12,62]

Contraception

The interactions between AEDs and oral contraceptive pills should be discussed with all women with epilepsy of childbearing age. Enzyme-inducing AEDs can hinder the effectiveness of oral contraceptives[63] (Table 2[64-73]), and women with epilepsy on enzyme-inducing AEDs should avoid combined oral contraceptive pills, combined contraceptive patches, progestogen-only pills, progestogen-only implants, and vaginal ring contraceptives.[2,74,75] Older-generation AEDs such as phenytoin, carbamazepine, phenobarbital, and primidone may belong to the enzyme-inducing category, but some newer-generation AEDs such as oxcarbazepine also have enzyme-inducing properties.[76] It may be advisable for women with epilepsy to use other contraceptive methods than the above-mentioned hormone-containing pills and devices because of the risk of contraception failure. If the use of oral contraceptives is unavoidable, hormonal contraception may be adjusted in women taking enzyme-inducing AEDs, although there is little evidence supporting this (Box[75,77]). As different cases are unique, it is advisable to consult specialists who have experience managing these conditions. Copper intrauterine devices, the levonorgestrel-releasing intrauterine system, and medroxyprogesterone acetate injections are less affected by enzyme-inducing AEDs.[2] Some opinions suggest more frequent injections of medroxyprogesterone acetate (every 10 weeks instead of every 12 weeks) in women with epilepsy taking enzyme-inducing AEDs because of potential interactions.[64] For emergency contraception, a copper intrauterine device should be advised. If the intrauterine device is not suitable or acceptable, a double dose of a total of 3 mg levonorgestrel can be given.[2,78,79] In contrast, serum lamotrigine levels can be reduced by simultaneous use of any oestrogen-based contraceptive, leading to deteriorated seizure control.[2] When the concomitant use of the contraceptive is stopped, the lamotrigine dose may need to be adjusted.[46]

Labour

Spontaneous vaginal delivery is not absolutely contra-indicated in most women with epilepsy. Only about 1% to 2% of women with epilepsy develop generalised tonic-clonic seizures during labour.[2]

TABLE 2. Common antiepileptic drugs and their main routes of elimination, enzymatic systems involved, and interactions with oral contraceptive pills[65]

AED	Main route(s) of elimination	Main enzymatic system(s) involved in metabolism	Interaction with OCPs
Carbamazepine[66]	Oxidation	CYP3A4 (active 10,11-epoxide metabolite cleared by epoxide hydrolase)	Significant
Lamotrigine[67]	Glucuronide conjugation	Glucuronyl transferase type 1A4	Significant
Oxcarbazepine[64]	Glucuronide conjugation (>50%) and renal excretion (<30%) (refers to the active metabolite MHD)	Glucuronyl transferases (refers to MHD)	Significant
Phenobarbital[64]	Oxidation + N-glucosidation (75%) and renal excretion (25%)	CYP2C9 and CYP2C19	Significant
Phenytoin[64]	Oxidation	CYP2C9 and CYP2C19	Significant
Perampanel[68]	Oxidation	CYP3A4	Significant at higher dosages
Topiramate[64,69]	Oxidation (20%-60%) and renal excretion	Inducible CYP isoforms (40%-80%)	Significant at higher dosages (>200 mg per day)
Ethosuximide[64]	Oxidation	CYP3A4	Probably insignificant
Gabapentin[70]	Renal excretion	None	Probably insignificant
Lacosamide[71,72]	Demethylation and renal excretion	CYP2C19, CYP2C9, and CYP3A4	Probably insignificant
Levetiracetam[73]	Renal excretion (75%) and hydrolysis (25%)	Hydrolase	Probably insignificant
Pregabalin[64]	Renal excretion	None	Probably insignificant

Abbreviations: AED = antiepileptic drug; CYP = cytochrome P450; MHD = monohydroxycarbazepine; OCPs = oral contraceptive pills

BOX. Possible measures for women taking enzyme-inducing antiepileptic drugs if oral hormonal contraceptives need to be used[75,77]

If combined oral contraceptives cannot be avoided, consider:
- at least 50 µg oestrogen dose
- tricycling (taking three packets back-to-back without a pill-free interval)
- reducing the pill-free interval to 4 days

If breakthrough bleeding occurs while using combined hormonal contraceptives, consider:
- increasing the dose of oral ethinylestradiol to 70 µg on specialist advice

The EURAP registry reported seizure occurrence in 3.5% of women with epilepsy in labour.[80] An epilepsy diagnosis per se is not an indication for elective Caesarean section or labour induction.[2] Antiepileptic drugs should be continued orally or intravenously. Measures such as adequate analgesia, including transcutaneous electrical nerve stimulation, nitrous oxide and oxygen, and regional analgesia, are recommended to reduce pain and emotional distress, but they may trigger seizures.[2] Pethidine, also known as meperidine, should be used with caution for analgesia during labour in women with epilepsy. Its metabolites may reduce the seizure threshold.[81] Caesarean section may be necessary if seizures are frequent or prolonged.[2] Seizures during labour should be terminated as quickly as possible to avoid maternal and fetal complications. Benzodiazepines are the drugs of choice,[2] and phenytoin can also be given intravenously.[82] Magnesium sulphate is a treatment option if a diagnosis of eclampsia is made.[2]

Some clinicians may prescribe vitamin K to women with epilepsy on enzyme-inducing AEDs in the last month of pregnancy to prevent haemorrhagic disease in the newborn. The usual dose is about 10 to 20 mg/day of oral vitamin K. There are insufficient data to fully support or refute maternal vitamin K prophylaxis.[2,7,83] It has been recommended that newborns of women with epilepsy be given 1 mg of vitamin K1 parenterally at delivery.[2]

Breastfeeding

There is no absolute contra-indication to breastfeeding by women with epilepsy who are taking AEDs.[2,84] However, mothers who take AEDs should be counselled about the potential risks of breastfeeding. Many AEDs are excreted in breast milk. The amount of drug absorbed by the infant depends on various factors, including the maternal plasma concentration, the degree of drug transfer to breast milk, and the amount of breast milk consumed by the infant. The degree of drug transfer to breast milk is inversely dependent on the drug's protein binding ability.[76] Primidone, levetiracetam, barbiturates, benzodiazepines, lamotrigine, gabapentin, topiramate, ethosuximide, and zonisamide probably have significant penetration into breast milk.[7,76,85,86] However, there is no evidence to show that indirect AED exposure through breastfeeding has clinically significant effects on offspring.[2,87,88] The potential risks of breastfeeding should be balanced by the benefits of breastfeeding for both the neonate and the mother.[84]

TABLE 3. Summary of epilepsy management issues in women with epilepsy

Preconception counselling and teratogenicity of AEDs
- All women with epilepsy should receive information about epilepsy and its treatment specific to her reproductive cycle.
- All women with epilepsy of childbearing age can be offered folic acid 5 mg daily.
- The risk of epilepsy in the offspring of women with epilepsy depends on the inheritance pattern of the individual epilepsy syndrome. The overall risk may be increased about 3-fold compared with the general population.
- AEDs can be teratogenic. Early ultrasound during pregnancy and other prenatal screenings for major congenital malformations are advisable.
- Valproate is associated with lower cognitive function in children with in-utero exposure. This risk may be related to dosage. However, valproate may also be effective against certain types of epilepsy, eg, juvenile myoclonic epilepsy. The risks and benefits of its use in patients of childbearing age or during pregnancy should be thoroughly discussed with patients and/or family to arrive at a joint decision.

Contraception
- Women with epilepsy taking enzyme-inducing AEDs and oral contraceptive pills may have reduced efficacy of contraception. Dose adjustment of oral contraceptive pills or alternative forms of contraception may be necessary.
- Serum levels of AEDs (eg, lamotrigine) may be lowered by oral contraceptive pills.

Pregnancy
- The majority of women with epilepsy have uneventful pregnancies. However, adverse outcomes for both mother and fetus occur relatively more frequently in pregnancies of women with epilepsy.
- Ultrasound scans are recommended to screen for major fetal malformations
- Monitoring of levels of AEDs (eg, lamotrigine) during pregnancy may help to guide dosage adjustment.
- Oral vitamin K1 10-20 mg/day may be given to mothers taking enzyme-inducing AEDs in the last month of pregnancy.

Labour
- Spontaneous vaginal delivery is considered to be safe in women with epilepsy in most cases.
- Elective Caesarean section may be appropriate if seizures are frequent.
- AEDs should be continued orally or intravenously.
- Newborns of women with epilepsy taking enzyme-inducing AEDs may be given vitamin K1 1 mg parenterally at delivery.

Breastfeeding
- Women with epilepsy should be counselled about the pros and cons of breastfeeding.
- Primidone, levetiracetam, barbiturates, benzodiazepines, lamotrigine, gabapentin, topiramate, ethosuximide, and zonisamide probably have significant penetration into breast milk.

Puerperium
- Sensible safety precautions may be taken to prevent seizure-related injuries.
- Serial serum AED level monitoring of the mother may be useful, and the AED dosage should be adjusted accordingly.

Menopause
- Hormone replacement therapy can significantly increase seizure frequency or interact with AEDs.

Catamenial epilepsy
- Seizures can cluster during different phases of the menstrual cycle.
- Women with epilepsy with suspected catamenial epilepsy should be advised to record the seizure attacks together with the menstrual pattern in their seizure diary.
- Intermittent benzodiazepines (eg, clobazam) during the susceptible phase of the menstrual cycle can be a treatment option.

Abbreviation: AED = antiepileptic drug

Puerperium

Women with epilepsy who have just given birth might face significant anxiety concerning the risk of accidents should they develop breakthrough seizures when they take care of their infants. While there is risk of injury to the infant, reassurance should be provided to the parents, as the actual risk level is probably low.[89] Safety precautions that are simple to implement could further reduce such risks significantly.[2] Mothers should breastfeed their babies while sitting on floor cushions to avoid dropping their babies should a seizure occur. If there is an aura, the mother should lay the baby down.[2] The mother bathing the baby in a bathtub by herself could potentially carry some drowning risk if a seizure occurs. The same risk also applies to the mother carrying the baby single-handedly.[46] Supervision by the partner or a caregiver may help to prevent injury to the baby should a seizure occur.[2] Information may also be given to parents early to facilitate preparation or home modification to provide an optimal environment to care for the newborn. Seizure frequency may be exacerbated during the postpartum period for reasons such as lack of sleep and drug non-compliance.[90] Serial serum AED level monitoring of the mother may be useful, as there may be physiological changes during the puerperal period, especially with certain agents such as lamotrigine.[57,91] Maintaining the serum drug level at approximately the pre-conception level is advisable, provided that the woman had good seizure control before the pregnancy.[51,92] Dosages of AEDs should be adjusted accordingly to avoid postpartum toxicity or deteriorated seizure control.[2]

Reproduction technology

With advancements in the field of reproduction technology, clinicians may receive questions on such technologies from women with epilepsy. Reproductive intervention may have implications

for women with epilepsy and their offspring. For example, ovarian stimulation with gonadotropin may induce seizure exacerbation in women with epilepsy.[93] Epilepsy is a heterogeneous disease entity, and although genetics play a part in its aetiology, it can have implications for many bodily functions. Single gene (ie, Mendelian) disorders account for only a small proportion of patients. The implications of these genetic factors in the offspring's life and development are often variable and complicated by many different factors. Reproductive options and application of reproductive technology, such as pre-implantation diagnosis, remain controversial. Whenever possible, cases should be referred to appropriate specialists, including geneticists and obstetricians, for proper counselling.

Menopause

Hormonal profile changes can affect seizure control in women with epilepsy.[94] Clinicians should remind patients that hormone replacement therapy can significantly increase seizure frequency during menopause, particularly in women with catamenial epilepsy.[95] Hormone replacement therapy (which entails the administration of exogenous female sex hormones) and contraceptive pills probably have similar drug interactions with AEDs.[96]

Catamenial epilepsy

Epileptic seizures may be triggered by serum hormonal changes. Catamenial epilepsy is characterised by an increased seizure frequency during certain phase(s) of the menstrual cycle compared with baseline. However, there is no uniform definition for it. The seizures can cluster in different phases, such as the perimenstrual, periovulatory, and luteal phases of the menstrual cycle.[97] Recognition of the catamenial seizure pattern can be challenging, as irregular menstrual cycles and anovulatory cycles are common. Women whose seizure occurrence is suspected to be related to the menstrual cycle should be advised to record the seizure attacks together with the phase of the menstrual cycle in their seizure diaries. Prolonged observation may be needed before a catamenial epilepsy pattern is recognised. Treatments include intermittent benzodiazepines (eg, clobazam) during the susceptible phase of the menstrual cycle.[98,99] Increasing the anticonvulsant dosage during susceptible periods of the menstrual cycle may also be feasible. Hormonal therapy has not yet been proven to be effective in general.[100] It may be beneficial in women with more frequent seizures around the perimenstrual period, especially in women with regular menstrual cycles.[101,102] However, further studies are probably needed before routine clinical use can be suggested.[100] Acetazolamide, used either daily or perimenstrually, may have benefits

for catamenial epilepsy, although the evidence to support its use is limited.[93,94,103,104]

Conclusion

New information has accumulated recently, providing new insight into the care of women with epilepsy and the implications for their offspring (Table 3). Thorough discussions with women with epilepsy may increase patients' levels of comfort and care, especially regarding major treatment decision on the issues of drug teratogenicity, neurobehavioral adverse effects on offspring, pregnancy, breastfeeding, contraception, reproduction technology, menopause, and catamenial epilepsy.

Author contributions

Concept or design: All authors.
Acquisition of data: RSK Chang.
Analysis and interpretation of data: RSK Chang.
Drafting of the manuscript: RSK Chang, KHK Lui, AWY Yung.
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All authors had full access to the data, contributed to the study, approved the final version for publication and take responsibility for its accuracy and integrity.

Disclaimer

This consensus statement is designed to assist clinicians by providing an analytical framework for treatment of women with epilepsy. It is not intended to establish a community standard of care, replace a clinician's medical judgement, or establish a protocol for all patients.

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