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Original Articles

Epilepsy in Women: Role of Paediatricians

KY ***LAU,*** KL ***KWONG***

Abstract Epilepsy is a common neurologic condition with important gender differences in the impact of the disease. Health care providers should discuss contraception and reproductive issues with all their female patients with epilepsy early as they enter puberty. Optimal care requires pre-pregnancy counselling, folate supplementation and discussion on risks related to pregnancy. Anti-epileptic drugs have been implicated as the major cause of teratogenesis, on the other hand, uncontrolled epilepsy is associated with maternal and fetal risk. Optimal seizure control with the lowest effective dose of antiepileptic drug is an important goal during pregnancy. Women with epilepsy should be counselled of breast-feeding and supported in their decision. Understanding the risks and appropriate management of both pregnancy and epilepsy in female patients is essential for the paediatricians. Pregnant women with epilepsy should be jointly managed by a team of professionals that includes neurologists, paediatricians, obstetricians and in some cases, geneticists.

Key words Epilepsy; Infants of epileptic mother; Women

A case of women with epilepsy (WWE) involving pregnancy and risk of congenital anomalies is presented. It illustrates the diverse challenges that paediatricians have to face. Areas of improvement would be addressed in the text.

Case Presentation

A 12-year-old girl presented to the Department of Paediatrics, Tuen Mun Hospital in 1994 with generalised tonic-clonic seizure. She was the product of a normal pregnancy, birth and delivery. She had normal developmental milestones. She enjoyed good past health. Carbamazepine was started after the second attack. Convulsions became more frequent, despite good drug compliance and an adequate drug level. She developed involuntary jerking of her upper extremities. Electroencephalogram showed bursts of generalised spike waves at 4 hz elicited on photic stimulation. The diagnosis was Juvenile myoclonic epilepsy. Anticonvulsant was changed to valproate. Seizure was then controlled. EEG in 2000 still showed generalised epileptiform discharge. She developed breakthrough seizure in 2000 in association with viral illness.

She worked in advertisement and cohabited with her boyfriend. She told the paediatricians that she wanted a baby and was ignored initially. She was then informed to look out for spinal cord defect if conceived. Folic acid was subsequently started. She was pregnant in 2001. Referral to obstetrics and medicals was made in the first trimester. The case was closed. She gave birth to a boy with renal malformations.

Epilepsy is a common chronic neurologic disorder, affecting 1% or more of the general population at all ages. There are clinically important gender differences in the impact of the disease. Epilepsy and antiepileptic drugs (AEDs) have the potential for far-reaching effects on the reproductive function and overall health of women. Some

Department of Paediatrics, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

KY **LAU** （劉潔如） *MRCP*
KL **KWONG** （鄺玲） *MRCP, FHKCPaed*

Correspondence to: Dr KL **KWONG**

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childhood epilepsies are not likely to remit, one example is Juvenile myoclonic epilepsy (JME) as illustrated by the case study. The condition typically presents in adolescence, is non-progressive, response to valproic acid is excellent and lifetime treatment is often necessary. Girls with epilepsy grow up into women with epilepsy. Paediatricians have to manage epileptic patients to at least 18 years old. Not to mention we have to look after infants of epileptic mothers (IEMs) who are at increased risk for adverse outcome.

In a survey by the British Epilepsy Association, 51% of WWE claimed to have never received advice on contraception, only 34% had ever discussed pregnancy with their physician, and less than 10% had received information about adverse effects of AEDs on fetal development.[1] A U.S. survey of physician practices reviewed that 4% of neurologists and none of the obstetricians were aware of the effects of the six most common AEDs on oral contraceptives.[2]

Counselling is crucial in the management of WWE and should be started early in puberty. Key topics to cover in counselling WWE are summarised in Table 1.[3]

Counselling Women with Epilepsy

Counselling at Puberty

Ovarian Hormone Influence

Many WWE experience changes in the phenotypic expression of epilepsy corresponding to the changes in reproductive status and over the reproductive cycles. Catamenial seizures are defined as at least 75% seizures occurring within 4 days preceding and 6 days after onset of menstruation.[4] Physiologically, this timing corresponds to periods of relatively high estrogen and low progesterone level. Counselling of catamenial epilepsy should include instruction on how to chart seizures, when to consider more detailed evaluations, and use of adjunctive medications or hormonal therapy to aid seizure control.[5]

Fertility

Menstrual cycle disturbances, hypergonadotrophic and hypogonadotrophic hypogonadism, polycystic ovaries, sexual dysfunction and reduced fertility are documented problems for WWE.[6-11] Fertility may be as low as two-thirds of that expected in general population.[9] Abnormalities of physiologic sexual arousal may lead to sexual dysfunction in WWE.

Contraception

There is an increased risk of oral contraceptives (OC) failure in women receiving drugs metabolised by the hepatic cytochrome P450 enzyme including phenytoin, primidone, carbamazepine, ethosuximide and barbiturates.[12,13] Enzyme-inducing drugs accelerate the metabolism of both estrogen and progesterone. Concentration of free progesterone can also be reduced as a result of elevated production of sex hormone binding globulin.[14] Women receiving enzyme-inducing AEDs should be treated with formulations containing 50 ug ethinyl estradiol or mestranol. The added risk of high dose of estrogen should be discussed. Barrier methods are recommended if breakthrough bleeding occurs.[15]

Table 1 Key topics to cover in counselling WWE

Access to care
Finding an appropriate health-care team
Establishing communications, roles, and power
Developing partnerships
Making informed choices
Identify health-care needs specific to WWE
Relationship between seizures and menstrual cycle
Effects of epilepsy on sexuality
Contraception
Fertility
Folic acid supplementation and teratogenicity of antiepileptic drugs
Pregnancy
Effects of pregnancy on epilepsy
Effects of epilepsy on pregnancy
Risk to mother
Risk to fetus
Breastfeeding
Menopause, hormone replacement, bone health
Cosmetic effects
Personal care and safety
Preventing injuries and assaults, safety management
Planning activities of daily living
Managing stress and other seizure triggers
Developing safe parenting skills
Social relationships and community living
Personal adjustment to epilepsy
Confidence, self-esteem, and body image
Disclosure of epilepsy
Social relationship

Pre-pregnancy Counselling

Women with epilepsy should receive counselling regarding effects of pregnancy on epilepsy and vice versa as they approach reproductive age. Preconception counselling is especially crucial in the management of WWE, paediatricians are urged not to wait for the patient to volunteer that she is planning a pregnancy as 50% of pregnancies in U.S. are unplanned.[16]

Seizure Control

Seizure frequency increases in one third of pregnant women with epilepsy.[17] Factors leading to breakthrough seizures include poor preconception seizure control, physiologic changes of pregnancy, vomiting, non-compliance, stress and sleep deprivation. Anxiety over fetal antiepileptic drug exposure and fears about breastfeeding are the most common reasons for non-compliance.[18] Counselling about the hazards of uncontrolled seizures may improve drug compliance.

Adverse Outcomes of Pregnancy

Over 90% of pregnant women with epilepsy had good pregnancy outcome. Even healthy parents have a 2-3% risk of having child with malformations.[19] All commonly used anticonvulsants have been associated with teratogenicity and there appears to be 4-8% risk of major birth defects in infants of epileptic mother (IEMs).[19] The risk is 2-3 times greater than that of general population. There is a great deal of overlap in the described dysmorphisms. Specific syndromes are no longer accepted, and the broader term, fetal antiepileptic drug syndrome, is more appropriate. Major congenital malformations include congenital heart defects, cleft lips and palates, neural tube defects (NTD), and genitourinary malformation.[20-24] Minor anomalies are observed in 10-30% of IEMs, these include craniofacial dysmorphism, distal digit and nail hypoplasia, minor skeletal anomalies, umbilical and inguinal hernias.[25] Prevalence of spinal bifida with valproate is 1-2% and 0.5% with carbamazepine.[24,26] However, a prospective study in the Netherlands found that IEMs exposed to valproate had a 5.4% rate of spinal bifida.[27] Fetal accumulation of toxic intermediate anticonvulsant metabolites, induction of folate deficiency and genetic predisposition are proposed mechanisms for antiepileptic drug teratogenesis.[28-31] The teratogenic potential of AEDs introduced in the last few years, including gabapentine, felbamate, lamotrigine, tiagabine, topiramate and vigabatrin remains to be delineated. Several studies have suggested an increased risk for reduced intelligence in children born to WWE.[32,33] However, as noted by Yerby, most studies did not control for parental intelligence and/or psychosocial environment.[34] Moreover, infants of WWE have decreased vitamin K and vitamin K-dependent clotting factors. Early haemorrhagic disease has been observed in neonates whose mothers were treated with enzyme-inducing drugs during pregnancy.[35] It is recommended that pregnant women with enzyme-inducing AEDs should be treated with oral vitamin K during the last month of pregnancy.[36]

Breastfeeding

Women with epilepsy initiate breastfeeding less frequently and discontinue breastfeeding earlier than women without epilepsy. Women in this study reported negative attitude towards breastfeeding on the part of their physician.[37] Antiepileptic drugs are known to appear in breast milk with level inversely proportional to degree of protein binding. Anticonvulsant level in neonate may reach therapeutic level.[37] Feeding difficulties, sedation, haematologic and or hepatic abnormalities in breast-fed infants of WWE taking AEDs have been reported.[38,39] Withdrawal symptoms after cessation of breastfeeding are also observed.[38] Women should be informed of the risk and benefits, encouraged to make individual choices and supported in their choices.

Management of Pregnancy in Women with Epilepsy

Management of epilepsy during pregnancy begins prior to conception. Verification of the diagnosis is imperative because persons with non-epileptic events can be treated erroneously with AEDs. Not all patients with epilepsy are best managed with medications. For example, surgical excision can be considered in mesial temporal sclerosis. No AED is absolutely safe. Those who care for WWE face a dilemma. Seizures needed to be prevented. Fetal exposure to medication needs to be minimised. The best AED for the individual patient needs to be determined. Seizure control is the goal of medical treatment. Antiepileptic drug discontinuation should be considered in women who have been seizure free for 2-5 years and have a single seizure type, normal neurologic examination, and normal electroencephalogram on treatment.[15] After drug withdrawal, an observational period of at least 6 months is advised before conception.[40] For those patients who are not candidates for drug discontinuation, whenever possible, polytherapy should be avoided.[41] Lowest effective serum

concentration should be maintained. Major change in drug therapy during pregnancy need to be avoided.

Accurate seizure classification is important so as to ensure appropriate treatment of seizure types and epilepsy syndrome. In JME, medications can be completely withdrawn in those with myoclonic jerk only and reinstated after first trimester. The role of lamotrigine is promising. Supplementation with at least 0.4 mg/day folate is recommended to all women of child bearing age. Recent studies have suggested that perhaps 0.5 mg or 0.6 mg/day folate might be more effective. Selenium, 0.1 mg/day, is also useful in reducing risk of congenital malformation.[42]

Pregnant women with epilepsy should be jointly managed by a team of professionals that includes neurologists, paediatricians, obstetricians and in some cases, geneticists. Women should be advised on the importance of proper sleep and drug compliance. Precipitating factors of seizures should be avoided. Serum antiepileptic drug level should be monitored at least once per trimester, and more frequently in those with frequent seizure, side effects or history of status epilepticus. Once the gestational age is established, a calendar can be planned for drug monitoring, pre-natal testing and vitamin K supplementation (Table 2).[43]

Regarding our patient with JME, counselling on contraception and teratogenic risks should be started early in puberty. Do not wait for the patient to volunteer that she is planning pregnancy. We should discuss on drug management and change it to lamotrigine at least 6 months prior to conception if patient prefers. Preconception folate should be started. The optimal drug level for seizure control should be determined and maintained throughout pregnancy. She should be advised on the importance of proper sleep and drug compliance. Precipitating factors of seizures should be avoided. Instead of just referring the patient to our medical and obstetrical colleagues, a team of professionals including neurologists, paediatricians, obstetricians and perhaps, the geneticists, should jointly manage the patient.

Conclusion

Managing WWE is a challenge. Counselling is crucial and should begin in early puberty. It is too late to wait for the patient to volunteer that she is pregnant. Management of pregnancy in WWE requires interdisciplinary approach. Paediatricians looking after infants of epileptic mother need to be aware of the adverse outcomes.

Table 2 Checklist of intervals for management of pregnancy in WWE

Preconception	Patient education
	Start folic acid supplementation
	Determine free AED level at which patient's seizure is controlled
First postconception visit	Review education
	Measure free AED level and folate level
	Determine expected date of conception
	Plan pregnancy follow-up visits
12th week GA	Anatomic ultrasonography
	Free AED level
15th week GA	Maternal serum screen
16th week GA	Free AED level
	Anatomic ultrasonography
20th week GA	Free AED level
24th week GA	Free AED level
28th week GA	Free AED level
32nd week GA	Free AED level
36th week GA	Free AED level
	Start vitamin K
	Plan for acute seizure treatment during labour and delivery
Delivery	Examine child for anomalies
4th week postpartum	Free AED level, watch for AED toxicity
8th week postpartum	Free AED level

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