Chapter 13
Epilepsy and Women

CQ 13-1

What kind of advice and information should be provided regarding pregnancy and childbirth for women with epilepsy?

Summary

For women with epilepsy, comprehensive counseling including guidance about pregnancy and childbirth should be provided in consideration of women's life cycle. Specifically, encourage adolescents to understand the basic and practical knowledge regarding pregnancy and childbirth as well as the knowledge about epilepsy including daily life and importance of treatment. Also, recommend planned pregnancy and childbirth to make these life events possible with the lowest risk. In patients who need to continue antiepileptic medication, it is desirable to select a drug with lower teratogenic risk and conduct appropriate dose adjustment to control seizures before pregnancy.

Comment

For women of childbearing age, it is desirable for the attending doctor to comprehensively assess the patient's capability of daily living based on the severity of epilepsy, environmental factors, and presence or absence of coexisting disability, and discuss with the family members, pediatrician and other health personnel to make a reasonable decision about the possibility of pregnancy and childbirth and to develop a plan for medication adherence[1-3]. Specifically, health professionals should provide advice and guidance to all women with childbearing potential starting from adolescence (junior high school students), at the timings appropriate to women's life cycle such as marriage and pregnancy, and recommend planned pregnancy and childbirth with strengthened cooperation from the family.

Regarding antiepileptic drugs (AEDs) during pregnancy and childbirth, we should be careful with the following points: (1) prescribe monotherapy in principle, (2) use the lowest required dose, (3) select AED with as low teratogenicity as possible, and (4) watch out for fluctuation in blood concentration of AED during pregnancy[2, 3]. Pay attention to the change in seizure frequency at each stage of pregnancy and childbirth, and aim at optimal AED therapy considering the balance between seizure control and reduction of risk to pregnancy and childbirth. In addition, give detailed explanations in advance on general precautions concerning pregnancy and childbirth, effects of AED on fetus and neonate, the course after childbirth, genetic inheritance of epilepsy, and development of the child. **Table 1** summarizes the measures to be taken concerning pregnancy and childbirth.

Although there is no clear difference in the rate of infants with congenital malformations between women with epilepsy not taking AEDs and the general population[4, 5], the frequency of congenital malformations in infants born from women taking AEDs during pregnancy is 4–10%, which is roughly 2–3 times higher than the frequency of 2–5% in the general population. The teratogenic risk varies depending on the AED being taken[2, 5, 6]. On the other hand, AEDs taken when not pregnant or AEDs taken by male patients have little effect on the fetus[2].

The types of congenital malformation are similar to those found in the general population, with high frequencies of cleft lip, cleft palate and cardiac anomalies. There are no clear differences among AEDs for minor anomalies, with one exception of spina bifida which is more often induced by valproate and carbamazepine[2].

When using oral contraceptives for planned pregnancy, explain their interactions with AEDs (phenobarbital, phenytoin, carbamazepine, and lamotrigine reduce the effect of contraceptives). We should recommend the patients to consult with an obstetrician or gynecologist for proper guidance about pills containing estrogen of 50 μg or more and other contraceptive methods[2, 7].

Furthermore, the experience of pregnancy and childbirth has great significance for women (and their families) in their lifetime. Therefore, we should follow the patients always considering psychological features.

In clinical practice, we may use charts such as that shown in Figure 1 to highlight points that require special attention at each stage of pregnancy, and also the drug adjustment plan.

References

1) Winterbottom J, Smyth R, Jacoby A, et al. The effectiveness of preconception counseling to reduce adverse pregnancy outcome in women with epilepsy: What's the evidence? Epilepsy Behav. 2009; 14(2): 273-279.
2) Kaneko S, Kan R, Tanaka M, et al. Treatment guideline for women of childbearing potential with epilepsy. Report of Japan Epilepsy Society Guideline Development Committee. Tenkan Kenkyu. 2008; 25: 27-31 (in Japanese).
3) Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. Epilepsia. 2013; 54(3): 405-414.
4) Fried S, Kozer E, Nulman I, et al. Malformation rates in children of women with untreated epilepsy: a meta-analysis. Drug Saf. 2004; 27(3): 197-202.
5) Veiby G, Daltveit AK, Engelsen BA, et al. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol. 2014; 261(3): 579-588.
6) Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008; 81(1): 1-13.
7) Perucca E, Battino D, Tomson T. Gender issues in antiepileptic drug treatment. Neurobiol Dis. 2014; 72(Pt B): 217-223.

Search formula and secondary reference sources

Search for the previous version of CQ13-1
PubMed search: June 28, 2015
epilepsy [mesh] AND (pregnancy [mesh] OR pregnant) AND "patient education" = 34

Ichushi search: June 28, 2015
((epilepsy/MTH) and ((pregnancy/TH or pregnancy/AL)) and ((patient education/TH or patient education/AL))) and (PT = excluding proceedings) = 12

PubMed search: June 28, 2015
epilepsy [majr] AND (pregnancy [majr] OR Delivery, Obstetric [mesh] OR lactation [mesh])Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 96

Ichushi search: June 28, 2015
((epilepsy/MTH) and ((pregnancy/TH or pregnancy/AL) or (childbirth/TH or childbirth/AL) or (breastfeeding/TH or breastfeeding /AL))) and (DT = 2008:2015 and PT = excluding proceedings) = 136

Table 1. Major measures for epilepsy patients of childbearing potential.

Before pregnancy	During pregnancy
(1) Adherence building with patient/family Conduct detailed counseling from before pregnancy Counseling items: · Basic knowledge of childbirth and pregnancy for women with epilepsy · Daily life and medication guidance · Recommendation of planned pregnancy and childbirth · Whether pregnancy and childbirth are realistic: explain importance of family cooperation · If necessary, also consider specialized psychological support (2) Doctor's judgement after consultation with patient · Possibility of dose reduction, adjustment or discontinuation of antiepileptic drugs (AED) · If drug taking is continued, use monotherapy at the lowest required dose possible · If using multiple drugs, pay attention to the combination Combination to be avoided: valproate + carbamazepine or phenytoin + primidone + phenobarbital Valproate should be avoided if possible; if must be given, use sustained release formulation aiming at a dose of 600 mg/day or less. · Folic acid supplement from before pregnancy (approx. 0.4 mg/day) · Collaboration with obstetrics/gynecology and pediatrics departments (cooperation from before pregnancy to after delivery preferable)	Regular visits and medication · Increase AED dose only when symptoms worsen despite regular drug taking · Measure α fetoprotein and folic acid levels at least once before pregnancy and as appropriate thereafter · α fetoprotein measurement at around 16 weeks' gestation · Perform fetal monitoring such as ultrasound at 18 weeks' gestation · In patients with generalized tonic-clonic seizures, pay attention to premature labor **At birth and puerperium** · In general, natural birth is possible · Pay attention to seizure worsening due to irregular drug taking before and after parturition **After birth** · Adjust AED dose if blood level fluctuates after childbirth · Breastfeeding is possible in principle (consider both mother and child factors comprehensively)

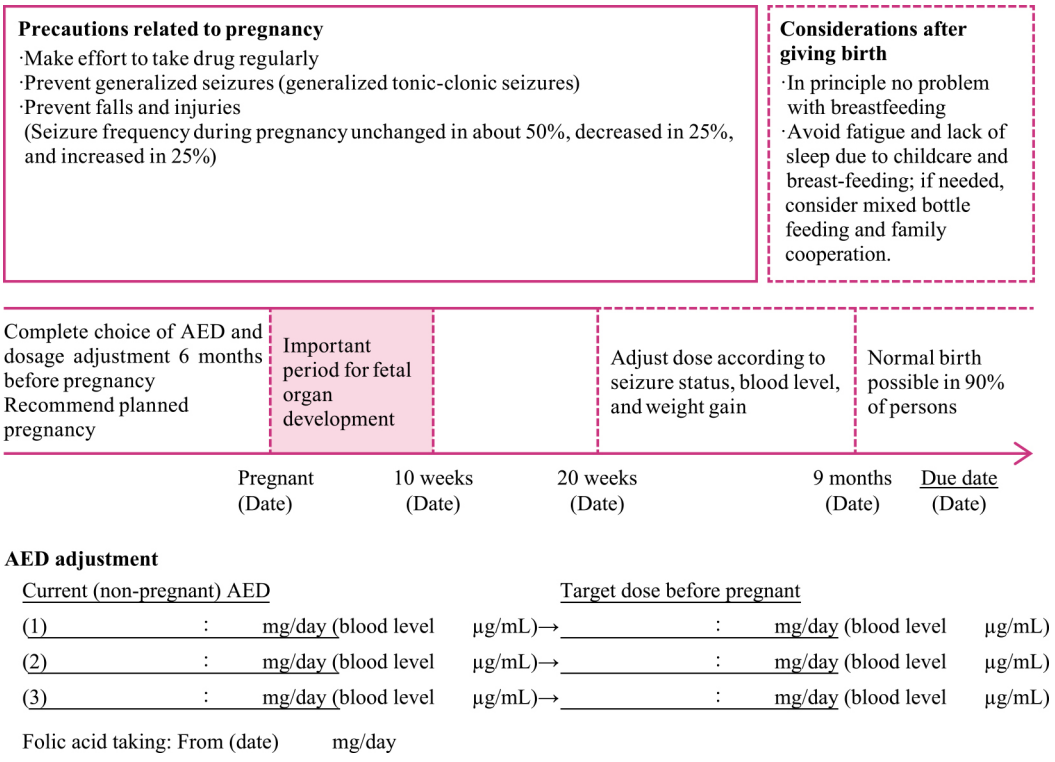

Figure 1. Points that require attention for pregnancy and childbirth
(Translated and modified from original figure of Ikeda A. Department of Epilepsy, Movement Disorders and Physiology, Kyoto University School of Medicine

CQ 13-2

What is to be noted for antiepileptic medication in women at childbearing age?

Summary

When pregnancy is expected, try to control seizures with antiepileptic monotherapy if possible. Also, select drugs with careful consideration for the risk of teratogenicity and cognitive impairment in children as well as the efficacy for seizure control. Also pay attention to dose adjustment.

Comment

In antiepileptic drug treatment, multidrug therapy has higher risk for teratogenicity than monotherapy, and the rates and types of malformation also vary depending on the types of drugs used in combination[1-3]. When antiepileptic medication is needed during pregnancy, aim at monotherapy as far as possible from before pregnancy and select drugs with low teratogenicity risk. The risk of major malformations for various antiepileptic drug are shown in **Table 1**[3]. Levetiracetam and lamotrigine have a low incidence of congenital malformation when used as monotherapy[3-5]. Carbamazepine also has a relatively low induction rate of malformation. Phenytoin, phenobarbital, and topiramate have slightly higher malformation induction rates[4]. Valproate has a higher malformation induction rate than the other drugs.

We should take note of the following point: even for antiepileptic drugs with low teratogenic risk when used alone, when these drugs are used in combination, the teratogenic risk increases depending on the combination[2, 4, 6]. For polytherapy, valproate, phenytoin, and phenobarbital are known to be drugs that increase the risk of teratogenicity when used in combination[2, 6]. Study has also shown that the teratogenic risk is increased when phenytoin or carbamazepine is used in combination with certain drugs including barbiturates (such as valproate + carbamazepine, and phenytoin + primidone + phenobarbital)[2].

In children born from a mother taking valproate during pregnancy, decrease of IQ (full scale IQ, especially verbal IQ) was found in a dose-dependent manner (especially at high doses of 1,000 mg/day or higher)[7]. The incidence of autism spectrum disorders also increased by prenatal exposure to valproate[8]. When using valproate, in addition to the high teratogenic risk, the risk of cognitive dysfunction and behavioral disorder in children should also be noted. When valproate needs to be taken unavoidably, we should prescribe it at a dose of 600 mg/day or lower as much as possible[7, 9]. Use of a sustained release formulation is desirable aiming to stabilize blood concentration[2]. International guidance also recommends that caution should be taken in the decision to prescribe valproate to pregnant women[9].

Regarding perampanel and lacosamide that have been launched on the market recently in Japan, there is currently insufficient data concerning human pregnancy and childbirth.

References

1) Borgelt LM, Hart FM, Bainbridge JL. Epilepsy during pregnancy: focus on management strategies. Int J Womens Health. 2016; 8: 505-517.
2) Kaneko S, Kan R, Tanaka M, et al. Treatment guideline for women of childbearing potential with epilepsy. Report of Japan Epilepsy Society Guideline Development Committee. Tenkan Kenkyu. 2008; 25: 27-31 (in Japanese).
3) Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. Seizure. 2015; 28: 46-50.
4) Vajda FJ, O'Brien TJ, Lander CM, et al. The teratogenicity of the newer antiepileptic drugs-an update. Acta Neurol Scand 2014; 130(4): 234-238.
5) Cunnington MC, Weil JG, Messenheimer JA, et al. Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology. 2011; 76(21): 1817-1823.
6) Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008; 81(1): 1-13.
7) 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): 244-252.
8) Christensen J, Grønborg TK, Sørensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013; 309(16): 1696-1703.
9) Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia. 2015; 56(7): 1006-1019.

Table 1. The prevalence of major congenital malformations caused by taking antiepileptic drugs.

	VPA	CBZ	LTG	PB	PHT	LEV	OXC	TPM
EURAP	9.7% (98/1,010)	5.6% (79/1,402)	2.9% (37/1,280)	7.4% (16/217)	5.8% (6/103)	1.6% (2/126)	3.3% (6/184)	6.8% (5/73)
NAAPR	9.3% (30/323)	3.0% (31/1,033)	1.9% (31/1,562)	5.5% (11/199)	2.9% (12/416)	2.4% (11/450)	2.2% (4/182)	4.2% (15/359)
UKIre	6.7% (82/1,220)	2.6% (43/1,657)	2.3% (49/2,098)		3.7% (3/82)	0.7% (2/304)		4.3% (3/70)
AUS	13.8% (35/253)	5.5% (19/346)	4.6% (14/307)		2.4% (1/41)	2.4% (2/84)	5.9% (1/17)	2.4% (1/42)
NMBR	6.3% (21/333)	2.9% (20/685)	3.4% (28/833)	7.4% (2/27)		1.7% (2/118)	1.8% (1/57)	4.2% (2/48)
SMBR	4.7% (29/619)	2.7% (38/1,430)	2.9% (32/1,100)		6.7% (8/119)	(0/61)	3.7% (1/27)	7.7% (4/52)

(Abbreviations: VPA: valproate, CBZ: carbamazepine, LTG: lamotrigine, PB: phenobarbital, PHT: phenytoin, LEV: levetiracetam, OXC: oxcarbazepine (not approved in Japan as of January 2018), TPM: topiramate)
EURAP: European and International Registry of Antiepileptic Drugs in Pregnancy, NAAPR: North American Antiepileptic Drugs and Pregnancy Registry, UKIre: UK and Irish Epilepsy and Pregnancy Registry, AUS: Australian Register of Antiepileptic Drugs in Pregnancy), NMBR: Medical Birth Registry of Norway, SMBR: Swedish Medical Birth Register
(Modified from: Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. Seizure. 2015;28:46-50.)

CQ 13-3

Is folic acid supplementation needed?

Summary

Folic acid supplementation is useful to prevent the occurrence of neural tube defect.

Comment

Some antiepileptic drugs are known to lower blood folic acid levels[1-3]. In particular, when valproate or carbamazepine is administered, supplementation of folic acid at an appropriate dose (0.4–0.6 mg/day)[3, 4] is desirable to reduce the risk of neural tube closure defect. It has also been reported that folic acid mitigates the adverse effect of antiepileptic drugs on IQ of children[5].

For administration, use of ready-made folic acid preparations or multivitamin preparations containing folic acid may be considered[1, 3].

■ References

1) Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and The Motherrisk Program. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007; 29(12): 1003-1013.
2) Wlodarczyk BJ, Palacios AM, George TM, et al. Antiepileptic drugs and pregnancy outcomes. Am J Med Genet A. 2012; 158A(8): 2071-2090.
3) Harden CL Pennell PB, Koppel BS. Practice Parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009; 73(2): 142-149.
4) Lifestyle-related Disease Control Office, Department of Community Health and Health Promotion Nutrition, Ministry of Health, Labour and Welfare. Promotion of appropriate information provision on the intake of folic acid by women of childbearing age for reducing the risk of neural tube closure defect. http://www1.mhlw.go.jp/houdou/1212/h1228-1_18.html (in Japanese)
5) Meador KJ, Baker GA, Browning N. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013; 12(3): 244-252.

CQ 13-4

Is it useful to monitor serum concentrations of antiepileptic drugs during pregnancy?

Summary

Since serum concentrations of antiepileptic drugs may change from the pre-pregnant values during pregnancy, it is desirable to conduct therapeutic drug monitoring (TDM) as necessary.

Comment

Serum concentrations of antiepileptic drugs may change during pregnancy. For example, serum concentration of lamotrigine may decrease to approximately 40% of the pre-pregnant level[1, 2]. Even though levetiracetam has a low serum protein binding rate, its serum concentration may decrease by 50% or more during pregnancy[3, 4]. Therefore, it is necessary to prevent the attenuation of seizure control effect of drugs by adjusting the doses appropriately based on serum concentrations measured at various appropriate times during pregnancy and at childbirth, using the optimal concentrations of antiepileptic drugs before pregnancy as the baseline level. On the other hand, it is important to prevent the adverse effects due to increase in serum concentrations after childbirth.

Attention should be paid to the interpretation of serum concentrations of protein-bound drugs such as phenytoin and valproate, because even when the total blood concentration shows a low value, the concentration of free drug may be increased due to decreased serum protein during pregnancy. Since the therapeutic effect of antiepileptic drug is mainly provided by the free drug, dosage should not be increased unnecessarily even when the total serum concentration decreases. If a reduction of free drug concentration is confirmed and seizures worsen despite good medication adherence, then consider increasing the dose of the drug[5].

References

1) De Haan GJ, Edelboek P, Segers J, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology. 2004; 63(3): 571-573.
2) Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2008; 70(22 Pt 2): 2130-2136.
3) Reisinger TL, Newman M, Loring DW, et al. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. Epilepsy Behav. 2013; 29(1): 13-18.
4) Wlodarczyk BJ, Palacios AM, George TM, et al. Antiepileptic drugs and pregnancy outcomes. Am J Med Genetics A. 2012; 158A(8): 2071-2090.
5) Røste LS, Taubøll E. Women and epilepsy: review and practical recommendations. Expert Rev Neurother. 2007; 7(3): 289-300.

CQ 13-5

Are women with epilepsy more likely to have complications during pregnancy?

Summary

Although the rate of complications is almost unchanged, some complications are increased slightly.

Comment

Injury caused by falls during seizure as well as intracranial hemorrhage, venous thrombosis, sinus thrombosis, and ischemic stroke attack could occur during pregnancy. Their frequencies are low and statistical figures are unknown[1-3]. There are few reports on premature rupture of membrane and umbilical cord abnormalities as complications at delivery. Over 90% of mothers affected by epilepsy have normal pregnancy and delivery.

According to a recent systematic review, the rates of complications including spontaneous abortion, preterm labor, perinatal hypertension, and postpartum hemorrhage, as well as the proportion requiring caesarean section were slightly higher in mothers with epilepsy than control mothers, but the incidence of events requiring intensive care was not different between these two groups[4].

References

1) Kaplan PW, Norwitz ER, Ben-Menachem E, et al. Obstetric risks for women with epilepsy during pregnancy. Epilepsy Behav. 2007; 11(3): 283-291.
2) Meador KJ, Pennell PB, Harden CL, et al. Pregnancy registries in epilepsy: a consensus statement on health outcomes. Neurology. 2008; 71(14): 1109-1117.
3) Aylward RL. Epilepsy: a review of reports, guidelines, recommendations and models for the provision of care for patients with epilepsy. Clin Med (Lond). 2008; 8(4): 433-438.
4) 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): 1845-1852.

CQ 13-6

Can women with epilepsy have a natural delivery? How are seizures treated during delivery?

Summary

In general, women with epilepsy can have a natural delivery. Seizures during delivery can be treated by the general strategy for epilepsy.

Comment

In most cases the patient gives birth by normal delivery[1-4]. In general, there is no indication for caesarean section, but caesarean section may be conducted depending on concomitant symptoms[3]. Vacuum-assisted delivery should be avoided[3].

Guide patients to continue regular drug taking as far as possible until birth[1-4]. If seizures occur during labor, they can be managed by the general strategy for seizures, but if necessary, administration of benzodiazepines is recommended.

We should pay attention to the withdrawal seizures in neonates because it sometimes occurs in neonates[3].

■ References

1) Røste LS, Taubøll E. Women and epilepsy: review and practical recommendations. Expert Rev Neurother. 2007; 7(3): 289-300.
2) Harden CL, Hopp J, Ting TY, et al. Practice Parameter update: Management issues for woman with epilepsy—Focus on pregnancy (an evidence-based review): Obstetrical complication and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009; 73(2): 126-132.
3) Kanemoto K, Kumatani S. Epilepsy treatment during pregnancy. Shinkei Naika. 2004; 61(1): 40-43 (in Japanese).
4) EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. Neurology. 2006; 66(3): 354-360.

CQ 13-7

Can women taking antiepileptic drugs breastfeed a baby?

Summary

They can breastfeed a baby.

Comment

Breastfeeding is in principle possible even when taking antiepileptic drugs. However, pay attention to the fact that antiepileptic drugs are transferred from maternal blood to breast milk at different rates[1-3].

When breastfeeding, observe symptoms in neonates such as withdrawal seizures, somnolence, hypotonia, and poor suckling, considering the transfer rate of the antiepileptic drug to breast milk and the half-life of the antiepileptic drug in the infant[3]. When these symptoms appear, manage in a flexible manner such as refraining from breastfeeding and measuring the serum concentration in the neonate[3]. **Table 1** shows the breast milk transfer rates of various antiepileptic drugs.

In any case, make realistic decision about breastfeeding based on a comprehensive assessment giving priorities to the child's mental and physical growth and the mother's wish. In addition, during the breastfeeding period, provide adequate care and guidance on daily life, including sleep deprivation and fatigue due to childcare.

■ References

1) Harden CL, Pennell PB, Koppel BS, et al. Practice Parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding. report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009; 73(2): 142-149.
2) Røste LS, Taubøll E. Women and epilepsy: review and practical recommendations. Expert Rev Neurother. 2007; 7(3): 289-300.
3) Kikuchi T, Yoshida S. Effect of child exposure to antiepileptic drugs via transfer of drugs to breast milk. In: Kaneko S, ed. The Course on Epilepsy, 3rd revised edition. Tokyo: Shinkoh Igaku Shuppansha Co., Ltd. 2012. p.215-218 (in Japanese).

Table 1. Breast milk transfer rates of various AEDs and half-life of AEDs in neonates.

AED	Transplacental transfer rate of AED	Breast milk transfer rate of AED	Half-life of AED in neonate (hours)
CBZ	0.69–0.78	0.36–0.41	8–36
CLB0.	1.7–7.5	13–0.36	17–31
CZP	0.59	1.0–3.0	13–33
DZP	1.2–2.0	0.5	31
ESM	0.97	0.86–1.36	32–38
GBP	1.74 (1.3–2.1)	0.7–1.3	14
LEV	1.14 (0.56–2.0)	1.0–3.09	16–18
LTG	0.9 (0.6–1.3)	0.61 (0.5–0.77)	24
OXC	0.92–1.0	0.5–0.65 1	7–22
PB	0.7–1.0	0.36–0.46	100–500
PHT	0.86–1.0	0.06–0.19	15–105
PRM	0.88–0.99	0.72	7–60
TPM	0.95 (0.85–1.06)	0.67–1.1	24
VPA	1.59–1.71	0.01–0.1	30–60
ZNS	0.92	0.41–0.93	61–109

Transplacental transfer rate = AED concentration in umbilical cord blood/AED concentration in maternal blood
Breast milk transfer rate = AED concentration in breast milk/AED concentration in maternal blood
(Modified from: Kikuchi T, Yoshida S. Effect of child exposure to antiepileptic drugs via transfer of drugs to breast milk. In: Kaneko S, ed. The Course on Epilepsy, 3rd revised edition. Tokyo: Shinkoh Igaku Shuppansha Co., Ltd. 2012. p.215-218.)