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Managing reproductive problems in women with epilepsy of childbearing age

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Abstract

Girls and women constitute nearly 50% of all epilepsy cases. Apart from the disease symptoms, epilepsy and antiseizure medications (ASMs) may also affect the reproductive function, pregnancy and even the health of their offspring. Therefore, it is very important to identify and summarize the problems and risks for women with epilepsy (WWE) of childbearing age, and offer internationally recognized methods through multidisciplinary collaboration. In this review, we summarize the reproduction-related problems with WWE and propose multidisciplinary management by epileptologists, gynecologists and obstetricians, as well as other experts, from preconception to delivery. Large, multicenter registries are needed to advance our knowledge on new ASMs and their effects on WWE and their offspring.

Keywords: Women with epilepsy, Reproduction, Antiseizure medications, Teratogenicity, Offspring, Seizure, Childbearing

Background

Epilepsy is a serious neurological disorder characterized by recurring seizures and accompanied by many comorbidities [1]. The estimated worldwide prevalence of epilepsy is 7.6 per 1000 persons [2]. In females the prevalence of epilepsy was estimated to be 3.45 per 1000 women in China, while that within childbearing age (20–40) in particular was 2.83–3.14 per 1000 women [3], which means that more than 3 million women with epilepsy (WWE) in China are facing reproductive problems. Two reasons can account for this problem. First, epilepsy and antiseizure medications (ASMs) have been verified to interact with regulations of sex hormones, leading to unsatisfactory seizure control and impaired reproductive function, particularly causing a polycystic ovarian syndrome (PCOS) that may lead to infertility in WWE [4]. Second, nearly one third of the patients taking ASMs are women of childbearing age, and almost half of them have unplanned pregnancy [5], thus putting themselves at risks of seizure attack during pregnancy and ASM-induced fetal malformation [6]. It has been reported that in UK the case fatality rate of WWE is much higher in the pregnant period than in the non-pregnant period [7], and the mortality rate of pregnant WWE is ten times higher than that of normal pregnant women [8]. Recent research on WWE further showed that some new ASMs such as the topiramate also have teratogenicity on fetus. In this review, we summarize the reproduction-related problems with WWE, update studies in WWE, and propose multidisciplinary management strategies for WWE from preconception to delivery.

Preconception period

Epilepsy and decreased fertility

According to a previous report, the infertility rate in WWE is 38.4%, which is two-fold higher than that in normal women [9]. The infertility rate in WWE is positively correlated to the number of ASMs used (7.1% in those with no ASM use, 31.8% with 1 ASM, 40.7% with 2 ASMs, and 60.3% with 3 or more ASMs) [9]. The most important factor causing infertility in WWE is reproductive endocrine disorders such as the polycystic ovary syndrome (PCOS), which occur more frequently in

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WWE than in women without epilepsy [10, 11], probably because of the interactions among epilepsy, ASMs and reproductive hormones [4] though the exact mechanism is unclear. There has been sufficient evidence for an impact of valproate (VPA) on the reproductive function of women with epilepsy, which would even cause PCOS through hyperandrogenemia and insulin resistance [12]. Thus, VPA exposure should be avoided in women of childbearing potential whenever possible [13]. Women with menstrual disorder, hirsutism and VPA therapy usually have a high probability of PCOS [14]. Another study has also shown a higher rate of PCOS in women with left temporolimbic epileptiform discharges compared with those with a right laterality and possibly with right-sided nontemporal discharges [15]. For women of reproductive age, PCOS screening as well as giving treatment on it is as important as seizure control, as PCOS has been reported to be closely associated with type 2 diabetes mellitus [16] and endometrial cancer [17]. However, during screening of PCOS, the circulating hormone level test and transvaginal b-mode ultrasonography need to be performed in WWE at early follicular phase (days 3–5 of the menstrual cycle) [11], which compromise the compliance of the patients. Therefore, every WWE should be informed that screening of PCOS is necessary and beneficial for their long-term prognosis. Once diagnosed, gynecologists should communicate with epileptologists and start treatments on PCOS. At the same time, epileptologists should modulate the therapy if necessary (e.g., reduce the dosage of VPA or replace VPA with other ASMs). So far the reproductive impact of other ASMs has not been sufficiently evidenced.

However, epilepsy itself as well as ASMs are not the only factors that lead to reproductive dysfunction in WWE. Psychiatry, family and society may also affect their reproductive health. Stigma, depressive disorder and anxiety appear to be more common in patients with epilepsy than in normal persons [18, 19]. WWE would even have an increase in births after epilepsy surgery [20]. These social psychological factors can affect the reproductive endocrine of WWE, and could be a prominent cause of reproductive dysfunction [21]. Thus, WWE should be recommended to psychologists and psychiatrists when needed. By this multidisciplinary management mode, WWE can be treated appropriately and have babies successfully.

Planning pregnancy

It is recommended that WWE become pregnant after seizure freedom and withdrawal of ASMs for 6–9 months, mainly because the best predictor of seizure control during pregnancy is the seizure control prior to pregnancy [22]. However, almost half of WWE had unplanned pregnancy [5], mainly resulting from the low contraceptive rate or contraceptive failure. Pharmacokinetic interactions between some ASMs and oral contraceptives (OCs) may result in not only decreased seizure control but also contraceptive failure. ASMs that can impair the contraceptive efficacy of hormonal contraceptives by increased clearance of the synthetic steroids include strong enzyme inducers like carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB) and primidone (PRM), and mild enzyme inducers like topiramate (TPM), oxcarbazepine (OXC), and felbamate [23]. On the other hand, OCs containing estrogen could decrease the concentrations of some ASMs such as lamotrigine (LTG), through enhancing their metabolism by UGT1A4 (an enzyme responsible for the glucoronidation of some ASMs by ethinylestradiol) [23]. The LTG plasma levels could be reduced by >50% during OCs co-medication [24] and increased by 84% after cessation of OCs [25]. Thus, epileptologists should ask their female patients if they are already using OCs and the type of OCs if any, before prescribing an ASM therapy. For women who must take enzyme-inducing ASMs or LTG to control seizures, continuous use of the hormonal contraceptive without a free interval may increase the contraceptive efficacy [26]. However, for women taking strong enzyme-inducing ASMs, additional protection such as barrier methods like condoms can be useful. In China, although the predominant contraceptive methods are intrauterine devices, sterilization and condemn [27–29], the use of OCs was increasing [27], to which epileptologists should pay more attention.

Folic acid

Generally, folate deficiency is associated with spontaneous abortion and developmental abnormalities in the offspring. Folic acid supplementation is associated with a lower risk of spontaneous abortion [30], better verbal outcomes [31] and a reduced risk of major congenital malformations [32] in fetus or postnatal babies women with epilepsy, In addition, women taking ASMs are at a higher risk of low serum folate compared to the general population, probably because that ASMs which could induce the cytochrome P-450 enzyme such as CBZ and PHT, could interfere with folate metabolism [33]. Thus, many guidelines have recommended folic acid supplementation from preconception to period during pregnancy, albeit with variations of the dosage and duration among different guidelines (Table 1).

A recent retrospective study of 153 pregnant WWE found that only 24% of them had folic acid supplementation before conception, among whom, only 13% began the supplementation 3 months prior to conception. More than one third of the WWE were never

Table 1 Recommendations for folic acid supplementation by different guidelines

Guideline	Recommendation for dosage	Recommendation for adding time
SIGN 2015 [34]	400 µg/day: not on ASMs 5 mg/day: on ASMs or not on ASMs, but high risk (with a family history of neural tube defects or a BMI > 30 kg/m^2)	From preconception and throughout the **first trimester** of pregnancy
RCOG 2016 [35]	5 mg	prior to conception and to continue the intake until at least the end of the **first trimester**
AAN/AES 2009 [36]	At least 0.4 mg/day	Prior to conception and during pregnancy
ETDP-EFA 2007 [37]	0.4 mg/day for nonpregnant women, 0.6 mg/day for pregnant women and those contemplating pregnancy, and 0.5 mg/day for lactating women. Many epileptologists recommend higher doses (0.8–4 mg/day) for women with epilepsy. However, for women with a family history of a neural tube defect, 4 mg/day is the recommended dosage.	Before conception and throughout pregnancy
NICE 2012 (update 2016) [38]	5 mg/day	Before any possibility of pregnancy

ASM Antiseizure medication, *AAN* American Academy of Neurology, *AES* American Epilepsy Society, *ETPD – EFA* Epilepsy Therapy Development Project – Epilepsy Foundation of America, *NICE* National Institute for Health and Care Excellence, *RCOG* Royal College of Obstetricians and Gynaecologists, *SIGN* Scottish Intercollegiate Guidelines Network

supplemented with folic acid throughout the pregnancy. The lack of knowledge on folic acid may account for this suppl failure, since over one third of them did not know that folic acid can decrease the risk of birth defect and 83.7% did not know the necessity of higher doses of folic acid supplementation in pregnant WWE [39]. Some patients even thought that folic acid could induce seizures and aggravate epilepsy. This fear is most likely from the Chinese drug instruction of folic acid, which states that "high doses of folate can antagonize the anti-epileptic effect of phenobarbital, phphenytoin and primidone, leading to an obvious decrease in the seizure threshold and an increase of seizure frequency in sensitive patients.". The instruction may be derived from the report of decreased plasma concentration of those ASM and increased seizure occurrence after high-dose (1–5 mg/day) supplementation of folic acid [40, 41], mainly because high levels of folate could increase the affinity of metabolizing enzymes, thus greatly enhancing the metabolism of the ASMs [42].

Recently, it has been reported that the offspring of rats receiving a high dose of folic acid before and during gestation have a 42% lower seizure threshold than the offspring of rats without folic acid supplementation, and in vitro acute application of folic acid or its metabolite 4H-folate to neurons induces hyper-excitability and bursting [43]. Another study found that a 20-fold higher intake of folic acid than recommendation was associated with embryonic delay and growth retardation, thinner ventricular walls in embryonic hearts, and susceptibility to embryonic defects [44]. However, the interaction between folic acid and new ASMs have been rarely reported. Therefore, as "of two evils, choose the less", folic acid supplement is highly recommended for WWE (4–5 mg/day) from 3 months prior to conception till the end of the first pregnancy trimester.

During pregnancy

Detrimental effect of ASMs on the offspring

As almost half of the WWE have unplanned pregnancy [5], a major task during pregnancy is to deal with the contradictory relationship between the teratogenicity of ASMs on fetus and the seizure control on mothers. Many ASMs have been verified to have teratogenicity in animal models [45–47]. The mechanisms may be that the active metabolites of ASMs can induce neuronal apoptosis or functional and physiological alterations in fetus [48–51]. Generally, polytherapy is associated with a higher teratogenic risk than monotherapy and VPA has the highest teratogenic risk among all the monotherapies [52–54]. Recently, a meta-analysis has also suggested that VPA or TPM exposure in uterus is highly associated with major congenital malformations (MCMs) in infants and children, while the odds ratio of MCMs is low in the offspring of women with uterus exposure to LTG or levetiracetam (LEV) [54]. The odds ratios of overall MCMs, separate MCMs, and common adverse obstetric outcomes of frequently-used ASMs, as obtained by meta-analysis, are shown in Table 2 [54].

A large retrospective study with 5374 births recently found that infants of mothers with epilepsy are at increased risks of stillbirth, having both medically indicated and spontaneous, preterm birth, being small for gestational age at birth, as well as having neonatal infections, any congenital malformation, major malformations, asphyxia-related complications, lower Apgar score, neonatal hypoglycemia, and respiratory distress syndrome compared with infants of unaffected women

Table 2 Odds ratios of different ASMs on major congenital malformations and other adverse prenatal outcomes [54]

	MCMs							Combined fetal losses	Prenatal growth retardation	Preterm birth
	Overall	Cardiac disease	Cleftlip/palate	Club foot	Hypospadias	Inguinal hernia	Undescended testes			
LTG	0.96 [0.72, 1.25] 6290	0.55 [0.32, 0.95] 4788	1.21 [0.45, 3.20] 4664	0.70 [0.12, 2.89] 1621	0.66 [0.23, 2.26] 95	0.86 [0.17, 5.92] 81	0.31 [0.05, 1.66] 1660	1.38 [0.70, 2.88] 2540	0.90 [0.56, 1.42] 2882	1.05 [0.70, 1.48] 3015
VPA	2.93 [2.36, 3.69] 4455	1.54 [0.98, 2.37] 3194	3.26 [1.38, 7.57] 2721	3.26 [1.43, 8.25] 802	2.58 [1.24, 5.76] 1437	1.64 [0.39, 10.02] 1845	1.10 [0.33, 3.78] 542	1.83 [1.04, 3.45] 2612	1.28 [0.86, 1.95] 1622	0.96 [0.65, 1.37] 1694
OXC	1.32 [0.72, 2.29] 372	0.69 [0.20, 2.18] 346	3.33 [0.66, 11.80] 304	2.40 [0.24, 13.37] 198	5.19 [0.95, 20.58] 200	1.17 [0.02, 17.89] 189	0.25 [0.00, 5.19] 182	1.66 [0.50, 4.50] 567	0.99 [0.56, 1.76] 1002	0.80 [0.51, 1.26] 1045
TPM	1.90 [1.17, 2.97] 599	0.66 [0.16, 2.11] 429	6.12 [1.89, 19.05] 429	1.77 [0.16, 11.44] 359	3.52 [0.77, 15.72] 429	1.52 [0.13, 14.90] 429	0.14 [0.00, 2.72] 359	23.58 [1.18, 549.60] 2	2.64 [1.41, 4.63] 472	1.38 [0.73, 2.35] 408
LEV	0.72 [0.43, 1.16] 1015	0.25 [0.03, 0.96] 754	0.48 [0.07, 2.18] 872	0.26 [0.00, 3.80] 450	0.29 [0.00, 2.56] 754	1.75 [0.22, 14.87] 1845	2.07 [0.38, 1221] 450	2.47 [0.50, 10.15] 28	1.27 [0.34, 3.54] 81	0.87 [0.31, 2.04] 93
CBZ	1.37 [1.10, 1.71] 8437	0.93 [0.62, 1.43] 1436	1.39 [0.56, 3.15] 5577	1.64 [0.68, 3.62] 99	1.09 [0.53, 2.61] 3540	1.54 [0.40, 8.78] 3307	0.53 [0.14, 1.96] 1386	1.25 [0.73, 2.36] 3911	1.15 [0.77, 1.67] 2897	1.10 [0.77, 1.56] 2141
PHT	1.69 [1.30, 2.17] 2237	0.99 [0.60, 1.57] 1697	3.11 [1.30, 7.72] 1172	2.73 [1.13, 6.18] 932	1.12 [0.51, 2.26] 1350	1.54 [0.38, 9.12] 878	1.27 [0.40, 4.38] 629	1.50 [0.85, 2.91] 618	0.68 [0.37, 1.21] 519	1.03 [0.55, 1.82] 283
PB	1.83 [1.35, 2.47] 1709	1.54 [0.96, 2.57] 1255	5.74 [2.41, 24.08] 894	1.38 [0.51, 3.42] 1057	1.53 [0.60, 3.84] 3824	1.21 [0.26, 7.54] 484	0.94 [0.27, 3.32] 526	0.90 [0.44, 1.93] 407	1.88 [1.07, 3.32] 400	1.59 [0.87, 2.75] 206

Each cell consists of three parts, odds ratio, [95% credible intervals], and number of cases; yellow cells mean the highest OR, pink cells mean the second higher OR, green cells mean the lowest OR

CBZ Carbamazepine, *LTG* Lamotrigine, *LEV* Levetiracetam, *OXC* Oxcarbazepine, *PB* Phenobarbitone, *PHT* Phenytoin, *TPM* Topiramate, *VPA* Valproate

[55]. However, in this study, ASMs use during pregnancy is not associated with adverse maternal and fetal or neonatal outcomes. And similarly, another study also found that ASMs are not associated with malformations in offspring [56]. Combined together, there are two reasons for the different conclusions concerning the effect of ASMs on offspring: first, LTG and CBZ account for approximately 77% of the therapies, whereas the more harmful ASMs such as VPA and TPM are used in only 19.2 and 4.0% of the pregnancies in the large retrospective study; second, both of the studies analyzed the MCMs rate of all ASMs together rather than analyzing the MCMs rate of each monotherapy.

On the other hand, some studies have suggested dose-dependent teratogenicity of some ASMs [57–59]. Tomson et al. found that LTG at < 300 mg/day correlates with the lowest rate of malformation (2%), while VPA doses ≥1500 mg/day are associated with a very high malformation rate (around 24%) [52, 58]. Thomas et al. also observed a dose-dependent teratogenicity of VPA (33.3% had MCMs at > 800 mg/day) [59]. Results of another large registry suggested that LTG at > 400 mg/day causes lower rate of MCMs than any VPA dose, although the result is not significant [53]. Nevertheless, the results may not be the same in Chinese WWE and their offspring since Asians have a lower body weight than Europeans on average. In a recent Chinese pregnancy registry of WWE, 5 of 155 pregnancies had MCMs (three congenital heart disease, one hydrocephalus and one meningocele) and four of the five mothers were taking ASMs during pregnancy. Also in this study, the newborns to women who received epilepsy surgery were more likely to get an Apgar score ≤ 7 [60].

Apart from fetus and infants, uterus exposure to some ASMs may also affect the long-term neurodevelopment of the offspring [61]. VPA exposure has been widely reported to be associated with dose-dependent decline of intelligence quotient (IQ), impaired verbal or nonverbal ability, impaired comprehensive or expressive language ability, impaired gross motor skills and autistic spectrum disorders in the offspring at the age of 2–14 years [62–69]. Exposure to clonazepam was associated with higher risk of microcephaly (OR 10.2, 95% CI 2.1–30.0) [70]. CBZ-exposed children have been reported to have impaired fine motor skills and social skills at age 1.5, increased aggressive symptoms at age 3 and reduced verbal ability at age 6 by a few studies [63, 66]. LEV-exposed children have impaired sentence skills and increased autistic traits at age 3, as reported by a study [66]. However, none of these studies were from Asia and commonly used ASMs for pregnant WWE, such as LEV and LTG, were rarely studied. Therefore, large multicenter prospective pregnancy registration of WWE and their offspring in Asia is needed.

Maternal seizure control

Uncontrolled seizures can impact on both fetal and maternal health [66, 71, 72]. As is indicated by previous studies, seizures still occur in 21.2–67.1% of WWE during pregnancy (Table 3) although the seizure frequency remains unchanged in 28–80% of the women (Table 4). As we can see, the percentage varies widely. On the one hand, different studies used different standards to define the word "unchanged" and used different periods as reference, and patients in each study had various kinds of ASMs. On the other hand, the changes of seizure

Table 3 Seizure occurrence rates in different studies

Study	Number of pregnancies	Study method	Center	Seizure rate/ ASM use								SDD	SE
				Total	LTG	VPA	CBZ	PB	PHT	LEV	OXC		
EURAP 2006 [78]	1956	Prospective registry	Multi (> 30)	41.60%	43.30%	23.80%	34.30%	29.00%	31.80%		58.50%	3.50%	1.80%
EURAP 2013 [72]	3784	Prospective registry	Multi (> 30)	33.40%	41.80%	25.00%	32.70%	26.60%				2.60%	0.56%
Thomas 2009 [79]	643	Prospective registry	Single	53.00%	44.40%	49.00%	56.70%	60.00%	66.70%			1.59%	0.47%
Vajda 2014 [73]	1111	Prospective registry	Multi (3)	–	51.30%	27.00%	37.80%			31.70%		–	–
Sabers 2009 [80]	42	Prospective registry	Single	46.00%	46.00%							–	–
Thomas 2012 [77]	1297	Prospective registry	Single	52.20%	CBZ PB PHT VPA CLB CLZ LTG LEV OXC PRM TPM							–	–
Cagnetti 2014 [81]	274	Prospective registry	Single	65.30%	CBZ LEV LTG OXC PB VPA							–	–
He 2017 [60]	155	Prospective registry	Single	67.10%	LEV VPA LTG CBZ OXC PHT TPM							9.68%	5.16%
Abe 2014 [82]	132	Retrospective	Multi (2)	27.30%	PB CBZ VPA CLZ CLB PRM DZP,ZNS							–	–
Reisinger 2013 [83]	115	Retrospective	Single	21.20%	LTG LEV CBZ TPM OXC PHT VPA ZNS ESM							–	–
Tomson 1994 [84]	89	Prospective registry	Single	45.00%	CBZ PHT CLZ PB PRM VPA ESM							–	–

ASM Antiseizure medication, *CBZ* Carbamazepine, *CLB* Clobazam, *CLZ* Clonazepam, *DZP* Diazepam, *ESM* Ethosuximide, *LTG* Lamotrigine, *LEV* Levetiracetam, *OCB* Oxcarbazepine, *PB* Phenobarbitone, *PHT* Phenytoin, *PRM* Primidone, *SDD* Seizure during delivery, *SE* Status epilepsy, *TPM* Topiramate, *VPA* Valproate, *ZNS* Zonisamide

Table 4 Seizure frequency change in different studies

Study	Study method	Center	Number of pregnancies	SF increased	SF decreased	SF unchanged	ASM use	Reference
EURAP 2013 [72]	Prospective	Multi (> 30)	3735	15.80%	12.00%	70.50%	CBZ LTG VPA PB	First pregnancy trimester
EURAP 2006 [78]	Prospective	Multi (> 30)	1956	17.30%	15.90%	63.60%	CBZ OXC LTG VPA PHT PB	First pregnancy trimester
Cagnetti 2014 [81]	Prospective	Single	274	23.40%	17.50%	59.10%	CBZ LEV LTG OXC PB VPA	Nine months before prepregnancy
Bardy 1987 [85]	Prospective	Single	154	32.00%	14.00%	54.00%	PHT CBZ CZP PRM ESM SLT PB VPA	Prepregnancy
Reisinger 2013 [83]	Retrospective	Single	115	38.30%	17.40%	44.30%	LTG LEV CBZ TPM OXC	Twelve months before pregnancy
Otani 1985 [86]	Prospective	Single	110	16.00%	4.00%	80.00%	PHT PB PRM CBZ VPA	Ten months before pregnancy
Tomson 1994 [84]	Prospective	Single	89	15.00%	24.00%	61.00%	CBZ PHT CLZ ESM PB PRM VPA	One month before pregnancy
Gjerde 1988 [87]	Prospective	Single	78	17.00%	17.00%	67.00%	CBZ PHT PB VPA PRM CLZ CLB	Prepregnancy
Sabers 2009 [80]	Prospective	Single	42	19.00%	10.00%	71.00%	LTG	Prepregnancy
Hoeritzauer 2012 [88]	Prospective	Single	39	30.80%	17.90%	51.30%	LEV	Prepregnancy
Pennell 2008 [89]	Prospective	Single	36	39.00%	33.00%	28.00%	LTG	Prepregnancy
La Neve 2015 [75]	Prospective case control	Single	36 (72 control)	19% (11%)	8% (7%)	72% (82%)	CBZ VPA	Prepregnancy

ASM Antiseizure medication, *CBZ* Carbamazepine, *CLB* Clobazam, *CLZ* Clonazepam, *ESM* Ethosuximide, *LTG* Lamotrigine, *LEV* Levetiracetam, *OCB* Oxcarbazepine, *PB* Phenobarbitone, *PHT* Phenytoin, *PRM* Primidone, *SF* Seizure frequency, *SLT* Sulthiame, *TPM* Topiramate, *VPA* Valproate

frequency during pregnancy are related to many factors, such as the seizure type, the type and number of ASMs, as well as the dose change of ASMs. Thus, it is necessary to establish an international standard on evaluating the seizure control and study the control effect of each ASM. From the existing evidence, LTG seems to perform worse in seizure control compared to both old and new ASMs during pregnancy, while LEV may perform best in controlling maternal seizures among new ASMs [72–75]. However, the most reliable predictor for seizure frequency during pregnancy is the seizure frequency before pregnancy, that is, women who had seizures before pregnancy are more likely to have seizures during pregnancy [60, 76, 77].

The increasing seizure frequency during pregnancy may be a result from the decrease of plasma ASMs [80, 83, 90], which may be attributed to the increased volume of distribution, declined plasma protein concentrations, increased renal clearance, and enhanced metabolism (e.g. glucuronidation and hydrolysis) during pregnancy [91, 92]. ASM clearance increases and plasma concentration decreases as pregnancy advance. This occurs especially for LTG, LEV and OXC [83, 91], which may be because of the strong enhancement of maternal glucuronidation and hydrolysis during pregnancy, through which the three ASMs are metabolized [91]. Different guidelines have different recommendations on monitoring the plasma concentration of ASMs during pregnancy (Table 5). As in China, WWE are mostly treated with ASMs which have obvious plasma level alterations, and thus have increased seizure frequency during pregnancy [60]. Therefore, we suggest routine monitoring of ASM concentration in women with a high risk of seizure occurrence.

A recent study found that withdrawal of or switch from VPA in the first trimester during pregnancy may result in a loss of seizure control [93]. Thus, epileptiologists should always be cautious when adjusting the type or dose of ASMs during pregnancy, and try best to control seizures with the minimum dosages of ASMs.

Table 5 Recommendations from guidelines on monitoring plasma concentration of ASMs during pregnancy

Guidelines	Recommendation
AAN/AES 2009 [36]	Monitoring should be considered routinely for LTG (seizure frequency is probably increased when 65% of target level is reached), CBZ, and PHT. Monitoring may be considered routinely for OXC and LVT.
NICE 2012 (update 2016) [38]	Monitoring is not recommended otherwise in routine. Monitoring is recommended if seizures increase or are likely to increase. Monitoring is recommended if dose needs to be adjusted (Lamotrigine and phenytoin are at risk of low serum levels).
ETDP-EFA 2007 [37]	Monitoring of ASM levels is needed throughout pregnancy. ASM levels should be monitored closely in the weeks following delivery since they may increase gradually. LVT, OXC, and LTG showed elevated levels with days of delivery.
RCOG 2016 [35]	Routine monitoring is not recommended although individual circumstances may be taken into account.
SIGN 2015 [34]	Routine monitoring of ASM concentrations is not indicated. Monitoring can be useful in the following circumstances: for adjustment of phenytoin dose, assessment of ASM adherence and suspected ASM toxicity.

Abbreviations: *ASM* Antiseizure medication, *AAN* American Academy of Neurology, *AES* American Epilepsy Society, *ETPD-EFA* Epilepsy Therapy Development Project-Epilepsy Foundation of America, *NICE* National Institute for Health and Care Excellence, *RCOG* Royal College of Obstetricians and Gynaecologists, *SIGN* Scottish Intercollegiate Guidelines Network

Perinatal period

The risk of pregnancy-related complications was once considered with no significant difference between pregnant WWE and pregnant women without epilepsy [76]. However, a retrospective study with 205 deliveries has suggested that WWE using ASMs during pregnancy have an increased risk of severe preeclampsia (odds ratio, 5.0), bleeding in early pregnancy (6.4), induction (2.3) and caesarean section (2.5) than women with no epilepsy, while women without ASMs use only had increased risks of forceps delivery and preterm birth [94]. Recently, the EURAP group has reported that WWE have higher risks of preeclampsia (adjusted relative risk, 1.24), infection (1.85), placental abruption (1.68), induction (1.31), elective cesarean section (1.58), and emergency cesarean section (1.09) than women without epilepsy. Nevertheless, they did not find a relatively higher risk of pregnancy and perinatal complications in women with exposure to ASMs during pregnancy, except for induction of labor (1.30) [55]. So far, whether ASMs play a role in pregnancy and obstetric complications remains uncertain, but a recent meta-analysis has suggested higher risks of spontaneous miscarriage (odds ratio, 1.54), antepartum hemorrhage (1.49), post-partum hemorrhage (1.29), hypertensive disorders (1.37), induction of labor (1.67), caesarean section (1.40), any preterm birth (1.16), and fetal growth restriction (1.26) in pregnant WWE [95]. Hence, WWE are likely to have a higher risk of pregnancy-related complications and cesarean section, and the high cesarean rate is often related to obstetric complications [56]. Therefore, epileptologists and obstetricians should pay attention to prevent those complications in pregnant WWE.

Additionally, women who were not taking ASMs often have a higher percentage of peripartum seizures (4.6%) compared to those on monotherapy (0.5%) or polytherapy (2.3%) [79]. In the case of a seizure, venous access should be prepared for timely administration of clonazepam or midazolam. In the case of generalized tonic-clonic seizures, continuous cardiotocography should be performed. The fetus should be monitored to prevent respiratory complications [96]. Thus, it is suggested that WWE deliver their babies at a hospital if they have the above conditions.

At birth, all infants of WWE taking enzyme-inducing ASMs should be provided with vitamin K1 (1 mg, intramuscularly) to prevent hemorrhagic diseases unless there are contraindications [97, 98]. If there are additional risk factors for hemorrhagic disease of the newborn (e.g., maternal liver disease, anticipated premature delivery), maternal administration of oral vitamin K1 (phytomenadione, 10 mg daily) in the third trimester of pregnancy should be considered [34].

It is recommended that WWE breastfeed their babies just like normal women, because the plasma concentration of ASMs in babies is low and causes no harm according to previous reports [99, 100], and breastfed children may even have higher IQ and enhanced verbal abilities [101].

Conclusion

While a girl or a woman is diagnosed as epilepsy, epileptologists should select the best therapy for her, and avoid ASMs that would affect the reproductive function (especially VPA), unless there is no better choice. Screening and treatment for reproductive disorders (such as PCOS) by a gynecologist are needed when a woman has

typical symptoms or high risks. Epileptologists should inform the patient that becoming pregnant after the seizure is controlled for 9 months is safer for both maternal and fetus health. They should also enquire the patient whether and what OCs she is taking, and then prescribe ASMs without interactions with OCs (such as LEV). Barrier method like condemn should be recommended if the patient must take enzyme-inducing ASMs or lamotrigine to control seizures. When considering pregnancy, ASMs with high fetal teratognicity (such as VPA or TPM) should be replaced with other ASMs like LEV and LTG. Patients should also be informed of folic acid intake at 4–5 mg/day from 3 months prior to conception till the end of the first pregnancy trimester, in order to prevent fetus malformation and spontaneous abortion. During pregnancy, monitoring the serum concentration of ASMs (especially LTG) is important for the control of maternal seizures with a minimum dose of ASM. At 18–20 weeks of gestation, obstetricians should offer the patient an ultrasound examination to assess the fetal anatomy and detect MCMs. One milligram of Vitamin K1 should be administered intramuscularly to newborns of women taking enzyme-inducing ASMs (such as CBZ, OXC and TPM), in order to prevent bleeding diseases.

Although there are many reproductive problems and risks among WWE, over 95% of them have experienced a normal process of pregnancy and have healthy offspring. The above-mentioned risks can be even lower after multidisciplinary management of WWE. However, the new-generation ASMs (such as LEV) have many unknown effects on pregnancy. The pregnancy registry is still the direction of future studies on the interaction between epilepsy and pregnancy. There have already been several large multicenter pregnancy registries in the North America, Australia, the United Kingdom, as well as the International Registry of ASM and Pregnancy [22]. It is very important to start such registry as soon as possible in China, or at least in Asia, in order to provide evidence of different ethnicities and help WWE have healthy offspring.

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Wanlin Lai reviewed the relative articles online and was a major contributor in writing the manuscript. Shixu He reviewed the articles online and participated in writing the manuscript. Professor Dong Zhou revised the manuscript for intellectual content. Professor Lei Chen revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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