



Impact of planning of pregnancy in women with epilepsy on seizure control during pregnancy and on maternal and neonatal outcomes



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ABSTRACT

Purpose: To investigate whether planning of pregnancy in women with epilepsy affects seizure control during pregnancy and to compare the maternal and neonatal outcomes in planned and unplanned pregnancies.

Methods: This was a retrospective cohort study of 153 pregnant women with epilepsy who were treated at the University of Tsukuba Hospital and Hokkaido University Hospital between 2003 and 2011. Twenty-one pregnancies were excluded due to insufficient data. Data of patients followed by neurologists during their planned pregnancies (planned-pregnancy group, $n = 51$) were compared to those of patients referred to neurologists after conception for managing epilepsy during pregnancy (unplanned-pregnancy group, $n = 81$). The treatment profile for epilepsy, seizure control, and maternal and neonatal outcomes in both groups were compared using Chi-square test or Fisher's exact test and Mann–Whitney U test.

Results: Compared to the unplanned-pregnancy group, the planned-pregnancy group showed a significantly greater proportion of patients receiving monotherapy with antiepileptic drugs (80% vs. 61%: planned vs. unplanned, $P = 0.049$) and those not requiring valproic acid (77% vs. 56%, $P = 0.031$). Furthermore, the frequency of epileptic seizures (16% vs. 35%, $P = 0.018$) and changes in antiepileptic drugs (24% vs. 41%, $P = 0.042$) were significantly lower in the planned-pregnancy group than in the unplanned-pregnancy group. No significant intergroup differences were noted in the obstetric complications and neonatal outcomes, including congenital malformations.

Conclusion: For women with epilepsy, planning of pregnancy is associated with good seizure control during pregnancy and less fetal exposure to antiepileptic drugs.

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1. Introduction

Population-based studies indicate that the prevalence of epilepsy in pregnant women is 0.7%, whereas registry-based studies suggest a range of 0.2–0.4%.¹ Thus, obstetricians often encounter cases of pregnancy in women with epilepsy (WWE) and

can be involved in the management of the pregnancies in these women as well as offer preconception counseling. In general, although the pregnancy outcomes in most WWE are favorable, epilepsy poses additional risks for the mother and fetus, including the potential effects of teratogenic antiepileptic drugs (AEDs), the effects of maternal seizures on the fetus, and genetic risks, all of which contribute to a two- to three-fold increase in the risk of adverse outcomes.² These adverse outcomes include major congenital malformation (MCM) in the fetus and long-term developmental delay.

A maternal seizure can directly affect the fetus and cause fetal hypoxia and distress. Additionally, adverse effects on the mother include falls; superficial abdominal hematomas; burns or other accidents; and significant obstetric sequelae, such as placental abruption and premature labor and delivery. Various complications of pregnancy have been reported in WWE. These women are at an increased risk of spontaneous abortion, induction of labor,

Abbreviations: WWE, women with epilepsy; AED, antiepileptic drug; MCM, major congenital malformation; VPA, valproic acid; PB, phenobarbital; CBZ, carbamazepine; PHT, phenytoin; VSD, ventricular septal defect.

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cesarean section, and postpartum hemorrhage³. Infants of WWE exposed to AEDs in utero are at a high risk of fetal growth restriction, preterm birth, low birth weight, and low Apgar scores.³

The incidence of fetal MCM in women without epilepsy is 1.6–2.2%,^{4–6} whereas that in WWE is higher, at 2.8–3.6%^{7–9} who take AEDs and at 4.2–6.7% who do not take AEDs.^{4,5,7–9} Furthermore, the risk of fetal MCM increases with the number of AEDs administered.^{5,6,9,10} In particular, treatment with valproic acid (VPA) in combination with AEDs is associated with a high risk of fetal MCM.¹¹ The teratogenic effects of most AEDs appear to be dose dependent,^{7,12} and numerous reports have confirmed this dose dependency in the case of VPA.^{7,9,10,13–15} Hence, transitioning from VPA to another AED should be considered before conception, and the lowest possible dose of the most appropriate AED should be administered before conception in WWE.

The Japanese guidelines for the management of WWE, as stipulated by the Societas Neurologica Japonica, recommend preconception counseling to provide detailed information about pregnancy and delivery in WWE and emphasize the importance of the medication during pregnancy, along with antenatal management involving the use of the lowest possible dose of the most appropriate AED, avoiding VPA, possibly withdrawing AED before conception, and supplementation with folic acid before and after conception to prevent neural tube defects.¹⁶ International guidelines recommend monotherapy with lamotrigine owing to its low risk of teratogenicity; however, this treatment option is currently not permitted by the Japanese national health insurance policy.¹⁶

Although various guidelines recommend planned pregnancy for WWE, the effects of planning remain largely unclear. Preconception counseling for WWE has been reported to be effective for reducing fetal MCM in children born to WWE receiving AEDs.¹⁷ However, the effects of a planned pregnancy on seizure control in WWE during pregnancy and maternal and neonatal peripartum outcomes have not been evaluated; in the present study, we aimed to evaluate these effects. Moreover, we aimed to compare the maternal and neonatal outcomes in planned and unplanned pregnancies in WWE.

2. Methods

We retrospectively reviewed the hospital records of 153 pregnancies in WWE who were treated at the University of Tsukuba Hospital (98 pregnancies) and Hokkaido University Hospital (55 pregnancies) between 2003 and 2011. Planned pregnancy was defined as the completed process of planning and preparing for pregnancy, during which the doses and numbers of AEDs and maternal physical health prior to conception were optimized by neurologists or neurosurgeons. According to the Japanese Healthcare system, all WWE taking AEDs should be followed up by their neurologists or neurosurgeons and not by general physicians, even if their seizures are well controlled, and some WWE who remain free of seizures without taking AEDs for a long duration are normally not followed by any medical doctor. Among WWE in the planned-pregnancy group, those who were regularly reviewed by their neurologists or neurosurgeons before conception received preconception counseling, epilepsy reassessment, AED dose adjustment; after successful execution of the planned pregnancy processes, their neurologists or neurosurgeons considered their conception appropriate. For WWE in the planned-pregnancy group who were not followed by medical doctors, neurologists or neurosurgeons consulted their conception, reviewed their condition, and considered pregnancy to be appropriate. The unplanned-pregnancy group included all the pregnancies not included in the planned-pregnancy group. WWE in the unplanned pregnancy group who were regularly followed up by their neurologists or neurosurgeons included those with

unexpected pregnancies (for both WWE and medical doctors) and those in whom the pregnancy had occurred during planning but not when conception was considered appropriate by the neurologists or neurosurgeons. The unplanned pregnancy group also included pregnancies of WWE who were not followed up by medical doctors and who did not consult neurologists or neurosurgeons about their pregnancy before conception. The planned pregnancy process was recorded on their medical chart or the introduction form administered at our hospital. The pregnancy was planned according to the discretion of the neurologist or neurosurgeon and was not structured, but it was in accordance with the guidelines for doctors authorized to treat patients under the Japanese government medical insurance system, as well as with the Japanese guidelines for the standard management of epilepsy. Data regarding the history of preconception treatment were unavailable in the case of 21 pregnancies, including medical letters from neurologists or neurosurgeons and medical interview forms; hence, these pregnancies were excluded from the study analysis. We classified the remaining 132 pregnancies on the basis of whether the pregnancy was planned or unplanned and compared the seizure control in pregnancy and maternal and neonatal outcomes in the 2 groups. Data were analyzed using the Chi-square test or Fisher's exact test and the Mann–Whitney *U* test, as appropriate. A *P* value of <0.05 was considered statistically significant.

The approval of the institutional review board and ethics committee was obtained at the University of Tsukuba Hospital (number: H23-62) and Hokkaido University Hospital (number: 011-0133). Informed consent was obtained from all patients.

3. Results

The planned-pregnancy group consisted of 51 pregnancies (39%), whereas the unplanned-pregnancy group comprised 81 pregnancies (61%).

3.1. Maternal backgrounds

Table 1 shows the patient demographics. Women in the planned-pregnancy group were significantly older (median age, 32 years; range, 17–42 years) than those in the unplanned-pregnancy group (median age, 28 years; range, 22–38 years; *P* = 0.012) (Table 1). The 2 groups showed no significant difference with respect to parity and gravidity (Table 1). Most women in both groups were Japanese. None of the women in the 2 groups had health conditions that were likely to affect maternal and neonatal peripartum outcomes, such as diabetes mellitus, hypertension, and hyperthyroidism. Only 1 woman in the unplanned-pregnancy group had asthma, which was well controlled. None of the women in the 2 groups had exposure to other teratogens except AEDs. Eight women in each group were overweight (BMI > 25), and the difference between the 2 groups in the proportion of overweight patients was not statistically significant (*P* = 0.32). Socio-economic

Table 1
Maternal characteristics.

	Planned	Unplanned	<i>P</i> -Value
Number	51	81	
Age	17–42	22–38	0.012 ^a
Nullgravida	20 (39.2%)	37 (45.7%)	0.47
Nullipara	29 (56.9%)	53 (65.4%)	0.32
BMI	16.9–38.3	14.3–32.8	0.15
Japanese	49 (96.1%)	79 (97.5%)	0.64
On welfare	1 (2.0%)	4 (4.9%)	0.65

^a *P* < 0.05, BMI: body mass index.

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