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Lamotrigine을 복용한 간질 여성의 임신 예후

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Pregnancy outcomes in women with epilepsy using lamotrigine

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Objective: The purpose of this study was to investigate pregnancy outcomes in women with epilepsy using lamotrigine (LTG).

Methods: We retrospectively reviewed the medical records of all patients who had been diagnosed as epilepsy and gave live singleton births in Yonsei University Health System, Seoul, Korea, between February 1996 and December 2007. Nine patients who were not taking antiepileptic drugs (AEDs) were excluded from this study. We subdivided the enrolled patients into 2 groups; patients exposed to LTG and others exposed to other AEDs. Congenital malformation, spontaneous abortion, small for gestational age, termination of pregnancy, intrauterine fetal death, preterm delivery, and adverse maternal outcomes were documented to evaluate the pregnancy outcomes. The statistical significance was defined as $P<0.05$.

Results: 129 cases were found in all medical records. The overall risk of congenital malformations in the AED group was 6.2% (n=8), which included 4 cases to carbamazepine (CBZ) monotherapy, 1 to valproate (VPA) monotherapy, and 3 to VPA+CBZ polytherapy. Congenital malformations were significantly increased in the non- LTG groups than in the LTG group (8.7% vs. 0%, $P=0.047$), especially in non-LTG polytherapy group (20.0% vs. 0%, $P=0.049$). The rates of spontaneous abortion, small for gestational age, termination of pregnancy, intrauterine fetal death, preterm delivery, and adverse maternal outcomes were no significant differences between the two groups.

Conclusion: This study demonstrates that administration of LTG in pregnant women with epilepsy could be more effective in decreasing teratogenicity than administration of other AEDs in polytherapy.

Key Words: Epilepsy, Antiepileptic drug, Pregnancy outcomes, Lamotrigine

Introduction

Epilepsy affects 0.5~1% of the general population. One-third of women of reproductive age, approximately 0.3~0.6% of pregnant women, are exposed to antiepileptic drugs (AEDs).[1] The majority of these pregnancies are uncomplicated, but it is known that there are increased adverse outcomes such as seizure (33%), vaginal bleeding (10%), fetal deformity (4~6%), preeclampsia, and extraction and cesarean delivery compared to women who do not take AEDs.[2] Risk of spontaneous abortion, intrauterine fetal death (IUFD), intra-

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uterine growth restriction (IUGR), and perinatal fetal death could increase in women with epilepsy compared to general population.[3]

The goal of epilepsy treatment during pregnancy is seizure control using AEDs, despite the fact that traditional AEDs are known teratogens. There have been insufficient studies on the relationship between obstetric complications, teratogenicity, and specific drugs. Furthermore, all of the reports were based on observations of traditional AEDs such as phenytoin (PTH), Phenobarbital (PB), carbamazepine (CBZ), and valproate (VPA). Lamotrigine (LTG) is a second-generation AED that is widely used for seizure control in epilepsy as well as in other neurologic and psychiatric disorders, and was approved by the US Food and Drug Administration for use as an AED in 1994.[4] The use of LTG increased dramatically between 1999 and 2003.[5] However, information on the safety of LTG in human pregnancy is still limited. There have been studies on teratogenicity of LTG that has a modest teratogenic risk compared to other AEDs, with reported rates of major congenital malformations from 1.0 to 5.6%.[5-10] Several observational studies have indicated that LTG clearance markedly increases during pregnancy,[11-14] with seizures worsening in women with epilepsy.[11,13]

The purpose of this study was to investigate pregnancy outcomes in women with epilepsy using LTG.

Material and Methods

A total of 138 patients with epilepsy who had antenatal care and gave births at Yonsei University Health System from February 1996 to December 2007 were enrolled in this study. Nine patients who were not taking antiepileptic drugs (AEDs) were excluded from this study. We subdivided the enrolled patients into LTG group and other AED group. Of 129 patients, 37 patients were exposed to LTG and 92 patients were exposed to other AEDs. We retrospectively analyzed their medical records to observe pregnancy outcomes including congenital malformation, spontaneous abortion, small for gestational age (SGA), termination of pregnancy, intrauterine fetal death (IUFD), preterm delivery, and adverse maternal outcomes. In women with epilepsy, seizures were classified by International League Against Epilepsy (ILAE).[15] Monotherapy was defined as a therapy with only 1 type of AED and polytherapy defined as a therapy with 2 or more AEDs. SPSS 12.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis, and statistical significance was calculated with chi-square test and *t*-test. A *P*-value <0.05 was considered statistically significant.

Results

One hundred twenty nine patients were exposed to AEDs. Of 129 patients, 37 patients were exposed to LTG and 92 patients were exposed to other AEDs. The mean of maternal age of LTG group and non-LTG group were 29.6 years and 30.2 years, respectively. The mean of gestational age at delivery of each group were 37.0 weeks and 37.5 weeks, respectively. Forty eight (37.2%) patients underwent cesarean section. Ninety women were exposed to monotherapy and 39 were exposed to polytherapy. There was no significant difference in maternal age, 1st trimester medication, and folic acid supplementation between LTG group and non-LTG group (Table 1). Twenty four (64.9%) patients were exposed to polytherapy in the LTG group and 15 (16.3%) patients in the non-LTG group with statistically significant difference. The most commonly used AEDs were CBZ (n=52), LTG (n=37), VPA (n=34), topramite (TPM) (n=24), phenytoin (PHT) (n=13), and oxcarbazepine (OCZ) (n=6). In non-LTG monotherapy, CBZ (n=39), VPA (n=13), PHT (n=11), TPM (n=5), OCZ (n=5), phenobarbital (PB) (n=2), clonazepam (n=1), and levetiracetam (n=1) were used. In polytherapy, LTG+TPM (n=9), LTG+VPA (n=7), LTG+VPA+TPM (n=4), LTG+CBZ (n=3), LTG+TPM+VPA

+levetiracetam (n=1), VPA+CBZ (n=5), VPA+TPM (n=3), VPA+CBZ+TPM (n=1), VPA+CBZ+OCZ (n=1), VPA+CBZ+PTH (n=1), CBZ+TPM (n=2), CBZ+PTH (n=1), TPM+levetiracetam (n=1) were used.

Out of 129 women with epilepsy, 8 (6.2%) experienced congenital malformation. Spina bifida, meningomyelocele, and congenital heart disesase (tricuspid regurgitation and pulmonary stenosis) were developed in women who were exposed to CBZ only. Spina bifida and anencephaly were developed in women who were exposed to VPA only. In women exposed to both CBZ and VPA, spina bifida, right finger agenesis, and long bone shortening were observed (Table 2). There were no multiple malformations. Of 6 termination cases, 3 cases were 1 right hand agenesis and 2 spina bifida.

Generalized tonic-clonic seizure, complex-partial seizure, partial seizure were found in 5 (13.5%), 0 (0%), and 3 (8.1%) patients respectively in LTG group, and in 15 (16.3%), 1 (1.1%), 1 (1.1%) patients respectively in non- LTG group. These findings were not statistically significant.

There was no significant difference in the incidence of spontaneous abortion, SGA, termination of pregnancy, IUFD, and preterm delivery and adverse maternal outcomes between LTG group and non-LTG group. However, there was a significant difference in the incidence of congenital malformation (0 vs.8.7%, P= 0.047).

Table 1. Patient characteristics (n=129)

Variable	LTG (N=37)	Non-LTG (N=92)	*P*-value
Age, years, mean±SD	29.6±3.0	30.2±3.3	0.349
Primigravida, n (%)	13 (35.1)	33 (35.9)	1.000
Previous cesarean delivery, n (%)	8 (21.6)	25 (27.2)	0.513
Gestational age at delivery, weeks, mean±SD	37.0±7.0	37.5±5.8	0.642
Cesarean delivery, n (%)	11 (29.7)	37 (40.2)	0.265
Medication method			<0.001
Monotherapy, n (%)	13 (35.1)	77 (83.7)	
Polytherapy, n (%)	24 (64.9)	15 (16.3)	
1st trimester medication, n (%)	30 (93.8)	89 (96.7)	0.722
Folic acid supplementation, n (%)	35 (94.6)	76 (82.6)	0.076
LTG dose, mg, median (range)	200 (50-400)		

LTG: lamotrigine, CBZ: carbamazepine, VPA: valproate, PTH: phenytoin, PB: phenobarbital, OCZ: oxcarbazepine, TPM: topiramate.

Table 2. Congenital malformations according to antiepileptic drug (AED)

Medication	Type of malformation
LTG monotherapy	None
CBZ monotherapy	Spina bifida, Meningomyelocele, TR and PS
VPA monotherapy	Anencephaly, Spina bifida
CBZ+VPA polytherapy	Spina bifida Right finger agenesis Long bone shortening
Total	8/129 (6.2%)

AED: antiepileptic drug, LTG: lamotrigine, CBZ: carbamazepine, VPA: valproate, TR: tricuspid regurgitation, PS: pulmonary stenosis, VSD; ventricular septal defect.

Between LTG monotherapy group and non-LTG monotherapy group, there was no significant difference in the incidence of congenital malformation. Congenital malformations were developed 5 cases in the non-LTG monotherapy group, but this finding was statistically insignificant. However, there was statistically significant difference in the incidence of congenital malformation between LTG polytherapy group and non-LTG polytherapy group. (0 vs. 20.0%, P=0.049) (Table 3).

One hundred eleven (86.0%) patients received a folic acid (4 mg/day) supplement during their first trimester. Among these women, 1 (0.8%) experienced spontaneous abortion and 1 (0.8%) had a fetal neural tube defect. In women without folic acid supplementation, 4 (26.7%) experienced spontaneous abortion and 2 (40.0%) experienced IUFD.

Discussion

The incidence of congenital malformation is 2~3 times higher in women with epilepsy compared to general population.[15] In our research, the risk rate of congenital malformation was 6.2%, which did not deviate much from the 6~8% of many other studies. When treatment is changed from polytherapy to monotherapy, the incidence of congenital malformation decreased from 13.5 to 6.2% or 9.6 to 7.6%, and the types of malformation changed to minor ones such as facial clefts, dysmorphia to spina bifida, and hypospadias.[16] Although there are some reports that polytherapy does not necessarily increase the induction of malformation,[17] the majority of studies have reported that polytherapy, especially with VPA, is related to an increase in the development of severe malformation.[18] According to the study of Dravet, spina bifida occurred in 1% of mothers taking VPA, and this result was 20% higher than in the normal population. There was a report that polytherapy with CBZ can increase spina bifida by 0.5~1%.[19]

The newly developed medicine called LTG has been studied to determine if it could replace VPA. In the case of monotherapy, the researches have been made with the 61 cases and 647 cases and it was reported that 0.0~4.4% of severe malformation occurred.[6,9] According to the study performed between 1992 and 2005 by the means of pregnant registration program, 2.8% of severe malformation had been observed in 707 cases, implying

Table 3. Adverse pregnancy outcomes in each antiepileptic drug

Outcome	Monotherapy			Polytherapy		
	LTG monotherapy (N=13)	Non-LTG monotherapy (N=77)	*P*-value	LTG polytherapy (N=24)	Non-LTG polytherapy (N=15)	*P*-value
Spontaneous abortion	0	1 (1.3%)	1.000	1 (4.2%)	0	1.000
Intrauterine fetal death	0	1 (1.3%)	1.000	0	0	
Termination of pregnancy	1 (7.7%)	1 (1.3%)	0.269	2 (8.3%)	2 (13.3%)	0.631
SGA	0	3 (3.9%)	1.000	2 (8.3%)	0	0.514
Preterm delivery	0	3 (3.9%)	1.000	0	1 (6.7%)	1.000
Placenta previa	0	2 (2.6%)	1.000	0	0	
PPROM	2 (15.4%)	2 (2.6%)	0.098	0	1 (6.7%)	0.385
Placental abruption	0	1 (1.3%)	1.000	0	0	
Adverse maternal outcomes*	2 (15.4%)	7 (9.1%)	0.613	1 (4.2%)	2 (13.5%)	0.547
Congenital malformation	0	5 (6.5%)	1.000	0	3 (20.0%)	0.049

LTG: lamotrigine, SGA: small for gestational age, PPROM: preterm premature rupture of membranes
*Adverse maternal outcomes: preeclampsia, placenta previa, PPROM, placental abruption

that LTG is a relatively low-risk drug compared to other AEDs.[16,20] In this study, congenital malformation did not occurred in LTG monotherapy group.

According to the British pregnant registration research, dosage effects of LTG have been observed. If the daily dosage was under 200 mg, 1.6% of severe malformation was observed whereas for a daily dosage of over 200 mg, the rate increased to 5.4%. In the turning point research by Sabers, the daily average dosage of 385 mg was administered to 137 mothers and the risk rate of malformation was 2.9%, proving that LTG is relatively lower in risk than other AEDs. In this study, women exposed to LTG monotherapy was 13. Except for 1 who experienced generalized seizure, the daily dose of the drug did not exceed 300 mg. Although there were 24 (64.9%) women exposed to AED polytherapy in the LTG group, no significant differences were observed between the LTG group and non-LTG group.

Obstetric complications were reported to be more common in women with epilepsy; include a low birth weight, preeclampsia, bleeding, placental abruption, and prematurity.[21-23] A study on the effect of seizure on pregnancy showed that convulsive seizure, especially in the form of generalized seizure, can cause hypoxemia and have a high death rate for both mothers and unborn children.[8] Teramo reported that a generalized seizure during labor can have a significant impact on fetal heart rate.[24] It has also been reported that the trauma caused by a seizure, especially uterine trauma, can damage the myometrium, resulting in the secretion of arachidonic acid that can induce uterine contractions or rupture of amniotic membranes causing the preterm delivery and the placental abruption could be induced.[25] According to a population-based study of Katz et al, higher rates of cesarean deliveries (17.3 vs. 11.55%, $P<0.008$), and gestational diabetes mellitus (9.1 vs. 5.5%, $P<0.02$) were noted among the epileptic population.[26] In this study, in non-LTG group, cesarean delivery rate was 40.2%, preterm delivery rate was 4.3%. All 4 cases of preterm deliveries were in non-LTG group. Moreover, one case of placental abruption happened in non-LTG group. The incidence of adverse maternal outcomes in the LTG monotherapy group was higher than in the non-LTG monotherapy group (15.4 vs. 9.1%). These results may raise concern about LTG's safety, but the sample size is too small to get wide confidence intervals.

It is important to emphasize parent counseling regarding the potential benefits and hazards of the treatment, including the uncertainty of long term adverse effects. Therefore, in the first stage of pregnancy, it is important to choose the proper AED to control seizure and maintain a minimum level of the drug in the serum. Additionally, taking folic acid to decrease the risk of congenital malformation, especially to decrease the risk of damage to the neural tube, is necessary. As the pregnancy progresses to term, it is important to prevent seizure by increasing AED level in the serum.[27] Monitoring the development of fetal malformation by means of maternal serum alpha-fetoprotein, estimation of amniotic fluid volume, and regular ultrasound exam should be performed as well.

LTG teratogenicity has proven inconclusive in human studies. There is a need to evaluate the possibility of minimizing fetal toxicity caused by drugs. To achieve this, a prospective study is warranted.

In conclusion, this study showed that administration of LTG polytherapy in pregnant women with epilepsy could be more effective in decreasing teratogenicity than administration of other combination of AEDs in polytherapy.

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= 국문초록 =

목적: 본 연구는 항간질약을 복용하는 간질 여성에서 lamotrigine 복용 여부에 따른 임신 예후를 조사하고자 하였다.

연구 방법: 1996년 2월부터 2007년 12월까지 본 병원에서 산전진찰을 시행 받고 분만한 총 138명의 간질 여성에 대해 후향적 연구를 시행하였다. 9명의 환자는 항간질약을 복용하지 않아 연구에서 제외되었다. Lamotrigine을 복용한 군과 Lamotrigine을 제외한 항간질약을 복용한 군으로 분류하여 선천성 기형, 자연 유산, 저체중출생아, 임신 종결, 자궁내태아사망, 조기 분만 그리고 불량한 산모 예후를 비교 분석하였다. 통계 분석은 유의확률이 0.05 미만일 때 유의한 것으로 보았다.

결과: 항간질약을 복용한 129명의 산모 중 8건 (6.2%)의 선천성 기형이 발생하였다. Carbamazepine 단일제제 사용 군에서 4건, valproate 단일제제 사용 군에서 1건, valproate와 carbamazepine 복합제제 사용 군에서 3건의 선천성 기형이 발생하였다. Lamotrigine을 복용하지 않은 군에서만 8건 (8.7%)의 선천성 기형이 발생하였고, 이는 통계학적으로 lamotrigine 복용 군과 유의하게 차이가 있었다 (P=0.047). 특히 복합제제와 단일제제 사용 군으로 나누어 비교하였을 때, 복합제제 사용 군 중, lamotrigine을 포함하지 않는 복합제제 사용 군에서 선천성 기형 발생이 유의하게 높게 나타났다 (P=0.049). 자연유산, 저체중출생아, 임신 종결, 자궁내태아사망, 조기 분만 그리고 불량한 산모의 예후는 두 군간에 차이가 없었다.

결론: 간질이 있는 여성에서 임신 중 Lamotrigine 복용은 복합제제 사용 군에서 다른 약제를 포함한 복합제제를 복용한 경우보다 선천성기형 발생을 감소시키는 데 더 효과적일 것으로 사료된다.

중심단어: 간질, 항간질약, 임신 예후, Lamotrigine