PROSPECTIVE SURVEILLANCE OF CROATIAN PREGNANT WOMEN ON LAMOTRIGINE MONOTHERAPY – ASPECTS OF PRE-PREGNANCY COUNSELING AND DRUG MONITORING

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SUMMARY – We prospectively surveyed 23 pregnant women with epilepsy on lamotrigine monotherapy and reported outcome of their pregnancies, including one fetal intrauterine death, one spontaneous abortion and two preterm deliveries. There were no congenital malformations in their offspring. Women with pregnancy planning and folic acid intake delivered babies with higher values of birth weight and birth length. There was large inter-patient variation during drug monitoring and in the need of dose adjustment. Individual approach to every woman and monotherapy with minimal effective lamotrigine dose with frequent drug monitoring enhances the possibility for successful pregnancy. The management of women with epilepsy should begin with pre-pregnancy counseling. Planned pregnancy enables periconceptional folic acid supplementation. Despite the small number of cases, these data indicate that la motrigine treatment during pregnancy might be relatively safe. Larger prospective studies are needed to obtain adequate power for statistical analysis including long-term cohort studies.

Key words: *Pregnancy – complications; Pregnancy – drug therapy; Epilepsy – drug therapy; Epilepsy – metabolism; Anticonvulsants – blood*

Introduction

Women with epilepsy are at a greater risk of complications in pregnancy, labor and adverse pregnancy outcomes than women without epilepsy. Teratogenic effects of all commonly used antiepileptic drugs (AEDs) in pregnancy have been recognized but relative risks of new AEDs and their long-term neurodevelopmental effects remain poorly understood. Some of the newer AEDs have not been used in large enough numbers to have meaningful data. In general, AED polypharmacy and higher blood levels of AEDs are associated with an increased incidence of birth defects in infants born to women with epilepsy. A single AED at the lowest possible dose for efficacy is recommended whenever possible[1].

All live-born children have 2-4 percent of risk to be born with some major malformation, but in women with epilepsy on one AED the incidence is 4-8 percent[2]. Methods of prenatal diagnostic testing offered to women with epilepsy should include measurement of maternal serum a-fetoprotein and level II fetal ultrasonography or amniocentesis, if warranted[3]. Major

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malformations most often found in children born to women with epilepsy are orofacial clefts, cardiac abnormalities and neural tube defects. Periconceptional folic acid supplementation may minimize the risk of neural tube defects in their offspring[3].

In many countries, national registries are being formed in order to collect new information on the possible teratogenicity of newer AEDs such as lamotrigine (LTG). The Australian Registry collected 68 pregnancies exposed to LTG and another AED and reported 3 children with different anomalies[4]. The North American AED Pregnancy Registry enrolled 564 women on LTG monotherapy during the first trimester of pregnancy: 15 newborns with malformations, 5 with cleft lip. Out of 1623 children exposed to LTG in another 5 registries, 4 had cleft palate or cleft lip (1:405 or 2.5/1,000) compared to 0.37/1,000 in the control group. These cases offered first information on the possible significant risk of cleft lip in children at *in utero* LTG exposure[5,6]. The UK Epilepsy and Pregnancy Register found 3.2% of major malformations from pregnancies on LTG; facial clefts were found in 0.2%, like in general population. The pregnancies exposed to LTG doses above 200 mg resulted in 5.4% of major congenital malformations[7]. Dolk *et al.* found no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to LTG monotherapy among 3.9 million births from 19 registries 1995-2005[8]. In their human pregnancy registry study, Cunnington and Tennis report that among 414 first-trimester exposures to LTG monotherapy, 12 (2.9%) cases presented with major birth defects, with no distinctive pattern of major birth defects being apparent among the offspring exposed to LTG monotherapy or polytherapy[9]. The Neurodevelopmental Effects of Antiepileptic Drugs Prospective Study found 1% of malformations in 98 mothers on LTG[10]. Until September 2007, the Lamotrigine Pregnancy Registry prospectively enrolled 1155 outcomes of pregnancies on LTG monotherapy: there were 2.7% of various major malformations, no association between LTG daily dose of 400 mg and frequency of malformations, and no higher incidence of orofacial clefts[11].

A greater incidence of mental retardation and/or microcephaly has been reported in children born to women with epilepsy or on particular type of AED, but these studies were inconsistent[12]. Factors other than maternal epilepsy that are thought to be important are maternal IQ scores and AED polypharmacy (particularly *in utero* exposure to methylphenobarbitone)[5]. There is no increased risk of early fetal death in women with epilepsy. Late fetal loss (stillbirth or spontaneous abortion after 20 weeks of pregnancy) shows an increased incidence in women with epilepsy, as much as twofold that in general population[2].

Good seizure control protects both the mother and the fetus. During pregnancy, one quarter to one third of women with epilepsy have an increase in seizure frequency despite continued use of AEDs. Decreased protein binding of AEDs, increased drug clearance, and increased maternal plasma volume during pregnancy may lower serum concentrations of AEDs. In the majority of pregnancies, there is a need for increase of LTG dosage and adjustment to previous dosage after delivery[13-15].

A favorable outcome of pregnancy in women with epilepsy on antiepileptic therapy can be achieved by pregnancy planning and preconception counseling involving a team of experts consisting of a neurologist, gynecologist, geneticist, etc. The preconception counseling, as a continuous process of planning and preparing for pregnancy and gaining optimal balance of physical, emotional and mental health before conception, could be one of the predictors of favorable outcome in such pregnancies.

Croatia is a Mediterranean European country with 4 million inhabitants. Since the foundation of two institutions in our country, Teratogen Information Service Zagreb (TIS Zagreb) and Center for Counseling in Epilepsy and Pregnancy in the year 2003, prospective data on pregnant women with epilepsy have started to be recorded systematically at our hospital based registry with the aim to establish safety of AEDs during pregnancy that are marketed in Croatia.

This was a prospective study designed to follow-up pregnancies in Croatian women with epilepsy treated with LTG and their offspring in order to provide additional data on the teratogenic risk of LTG and to assess the effects of preconception counseling in such pregnancies and significance of drug monitoring during pregnancy.

Materials and Methods

Study design

All pregnant women were recruited for the study from the Center for Counseling in Epilepsy and Preg-

nancy, University Department of Neurology, Sestre milosrdnice University Hospital, during a 5-year period (May 2003 – May 2008). Our Center has a multidisciplinary team of medical professionals – neurologists, gynecologists, pediatricians and genotoxicologist. All women were enrolled in the study in the first trimester of pregnancy. Most of them had been surveyed at the same hospital before their index pregnancies occurred, and one third presented for the first time in the Center for Counseling during pregnancy. All study women were surveyed prospectively during their pregnancy and all were taking LTG throughout pregnancy. All newborns were examined and followed-up to at least one year of age by neuropediatricians and clinical geneticists at University Department of Pediatrics in the same hospital. All pregnant women with epilepsy were controlled by a gynecologist in the same hospital and delivered at Maternity Unit, Sestre milosrdnice University Hospital.

This survey was the first phase of an ongoing prospective study in Croatia including pregnant women with epilepsy treated with all types of AEDs and long-term follow up of their offspring till school age in order to assess long-term neurodevelopmental effects of newer AEDs.

Study population

A total of 23 pregnancies under LTG monotherapy were enrolled during the period of 5 years (May 2003 – May 2008). The data obtained from pregnant women included their age, history of previous abortions or children with congenital malformations, parity, type and duration of epilepsy, and types and doses of AEDs before pregnancy. Data on current pregnancy included information on pregnancy planning, periconceptional folic acid intake, frequency of seizures, and adjustment of AED doses during pregnancy with final outcome of pregnancy. The data collected after pregnancy included adjusted AED doses, if needed.

The 'periconceptional' folic acid intake in women with epilepsy referred to folic acid intake at least 4 weeks before pregnancy and during pregnancy. The term 'pregnancy planning' refers to the woman's decision to achieve pregnancy and consideration of changing dietary habits prior to conception.

The information collected on newborns included gestational weeks at delivery (Farr evaluation), Apgar score, birth weight and birth length, neuropediatric evaluation and detailed clinical examination by clinical geneticist in order to exclude major and minor congenital malformations. Further investigations, if needed, included brain ultrasound, karyotyping, cardiologic evaluation, etc.

All live births were prospectively surveyed by two hospital neuropediatricians till the first year of life in order to exclude other possible congenital malformations (some congenital heart malformations, genitourinary tract malformations) and neurodevelopmental effects of AEDs.

Statistical analysis

Data were presented as mean ± standard deviation (SD). Due to the small sample size, comparisons between the means of values from pregnancies with favorable outcome and pregnancies with adverse outcomes and between the means of values in pregnant women with and without folic acid supplementation were made by use of two-tailed Student's *t*-test. A $P<0.05$ was the criterion for difference significance.

Results

Sociodemographic/reproductive characteristics and pregnancy planning

During the 5-year period (May 2003 – May 2008), 23 Croatian pregnant women with epilepsy on LTG monotherapy were enrolled. Pregnant women were all Caucasians, with no ethnic differences. The mean age of women with epilepsy was 27.14±3.15 years. Of 23 women, only 4/23 had graduated at university, while most of them (17/23) had medium educational level (secondary school) and 2/23 had low educational level (elementary school). Most of them were married (22/23), with average family income (19/23). In 11/23 women it was the first pregnancy, 3/23 had previous spontaneous abortions, and none had a child with congenital malformation (Table 1). Eleven of 23 women planned their pregnancies and 16 took folic acid during the periconceptional period. Four women were smoking throughout pregnancy and they all delivered healthy newborns. None of the study women reported alcohol consumption.

Drug monitoring during pregnancy

Seventeen of 23 women with epilepsy under LTG had favorable outcome of pregnancy and delivered

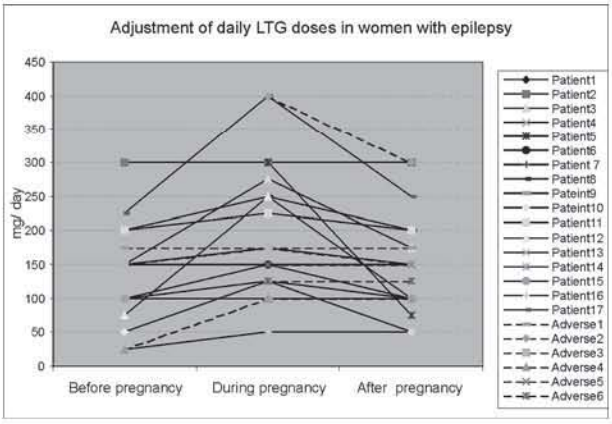

Fig. 1. Adjustment of daily lamotrigine (LTG) doses in women with favorable and adverse pregnancy outcomes

healthy newborns. In 4 of these 17 patients, AED had been switched to LTG short before pregnancy, whereas 13 women had been treated with LTG for a longer period before pregnancy.

In the group of women with favorable pregnancy outcome, the mean daily dose of LTG before pregnancy was 135 mg (range 25-300), during pregnancy 200 mg (range 50-400), and after pregnancy 141 mg (range 50-300). Adjustment of the daily dose of LTG was required in 13/17 patients, and in 10 of them more than once during pregnancy. The LTG dose adjustment was mostly done during 4th and 5th gestational month: for seizures accompanied by low plasma LTG concentration during pregnancy in 8 women and for low LTG concentration in another 5 women. Data on LTG dose adjustments during and after pregnancies in study women are presented in Fig. 1. These data reflect the high inter-individual variability in the need for dose adjustment among all women. Dose adjustment was mostly required between 4th and 5th gestational month. Six women with adverse outcomes are presented on Fig. 1 with dashed lines, and 4 of them with almost linear dashed lines. Due to the short duration of their pregnancies, there was no need for adjustment of LTG dose. The same reason could explain the slight, but not statistically significant differences in the mean percentage of dose adjustment during pregnancy between women with favorable outcome and those with adverse outcome (47% of previous dose in women with favorable outcome *vs.* 24% of previous dose in women with adverse pregnancy outcome) (P=0.1619, 95% confidence interval, t=1.4318, df=32, standard error of difference = 16.516) and also slight, statistically non-significant differences in the mean percentage of dose readjustments after pregnancy (24% *vs.* 7%) (P=0.0935). The majority of LTG doses after pregnancy needed to be readjusted during 8 weeks after pregnancy, but the values of LTG still remained higher than those before pregnancy. The mean daily dose of LTG during pregnancy in 6 women with adverse pregnancy outcome was 188 mg and after pregnancy 150 mg.

The maximal daily LTG dose of 400 mg during pregnancy was the same in both groups of women with epilepsy, but there were differences in maximal LTG doses during pregnancy between the two groups. Most pregnant women with adverse outcome did not cross the preferred LTG daily dose of 200 mg, whereas even 7/17 women with favorable outcomes did.

Table 1. Sociodemographic/reproductive characteristics, pregnancy planning and folic acid supplementation in women with epilepsy on lamotrigine therapy

Characteristics	Patients N=23
Age (yrs)	27.14±3.15
Education	
University	4
Secondary school	17
Elementary school	2
Marital status	
Married	22
Divorced	0
Single	1
Family income	
Above average	2
Average	19
Below average	2
Parity (No. of children)	
0	14
1	7
2 and more	2
Spontaneous abortions in previous pregnancies	3
Planned pregnancies	11
Periconceptional folic acid intake	16
Smoking	4
Alcohol consumption	0

Table 2. Outcome of pregnancies with antiepileptic drug (AED) therapy switch short before pregnancy

Patients with epilepsy N=7	AED before pregnancy	Max LTG during pregnancy	Max LTG after pregnancy	Pregnancy planning/FA intake	Seizure deterioration	Outcome
1	VPA	300	200	Yes/Yes	Yes	Live birth
2	PHT	100	100	Yes/Yes	No	Live birth
3	CBZ	250	200	No/Yes	No	Live birth
4	VPA	150	150	No/No	No	Fetal intrauterine death
5	CBZ + MPB	400	300	Yes/Yes	Yes	Preterm delivery, hypotrophic neonate
6	VPA	125	125	Yes/Yes	No	Spontaneous abortion in 7th week, toxoplasmosis
7	TPM	125	100	No/Yes	No	Live birth

VPA, valproic acid; PHT, phenytoin; CBZ; carbamazepine; MPB, methylphenobarbitone, TPM, topiramate

Seven women were treated with other types of AED short before pregnancy: 3 with valproic acid (VPA), another 3 with monotherapy including topiramate (TPM), phenytoin (PHT) and carbamazepine (CBZ), and 1 with CBZ and methylphenobarbitone (MPB) (Table 2). In all of them, the previous AED therapy was switched to LTG short before pregnancy. Two of them had seizures during pregnancy and half

Table 3. Drug adjustment and pregnancy outcome in women with seizures during pregnancy (n=8)

Patients with seizures N=8	AED before pregnancy mg/day	Max LTG during pregnancy mg/day	Max LTG after pregnancy mg/day	Pregnancy outcome
1	LTG 150	275	175	Live birth
2	VPA	300	200	Live birth
3	LTG 200	225	200	Live birth
4	LTG 75	125	50	Live birth
5	CBZ + MPB	400	250	Preterm delivery, somatic hypotrophy
6	LTG 150	175	150	Preterm delivery, Apgar 7/8
7	LTG 100	125	100	Live birth
8	LTG 225	400	300	Live birth

AED, antiepileptic drug; LTG, lamotrigine; VPA, valproic acid; CBZ; carbamazepine; MPB, methylphenobarbitone

of pregnancies were planned. Four of these 7 women had adverse outcomes of pregnancies *versus* 2/16 women that had been already treated with LTG for a longer period before pregnancy.

Eight women had seizures during pregnancy, but they all delivered live-births (Table 3). The only adverse outcomes in the group with seizures were 2 preterm deliveries: one child was healthy and another one, with Apgar 7/8, had moderate neurodevelopmental delay during follow up, but was successfully rehabilitated in our hospital. These two women with preterm deliveries did not have higher frequency of seizures than another six women with seizures that delivered on term.

In 23 study women, there was no case of maternal toxicity due to higher plasma concentration of LTG.

Pregnancy planning and periconceptional folic acid intake

Nine of 17 women with favorable outcome planned their index pregnancies, but due to preconception counseling and repeated recommendations for folic acid intake during therapy with AEDs, even 13/17 women took folic acid during proper periconceptional period. Women with folic acid intake delivered babies with significantly higher values of birth weight than those without folic acid supplementation (P=0.0066, t=3.1472, df=15, standard error of difference = 226.756), and also significantly higher values of birth length (P=0.0409, t=2.2367, df=15, standard error of difference = 0.748). There was no statistical significance for gestational weeks between the two groups (P=0.3791, t=0.9064, df=15, standard error of difference = 0.382) (Table 4).

In 6/23 women, the outcome of pregnancy was adverse (Table 5): one had elective termination of pregnancy because of spontaneous abortion just before the index pregnancy and unplanned index pregnancy; one had intrauterine fetal death in 20th week without evidence of infection, genetic disease or congenital malformation; 2 had spontaneous abortion, but one of them was diagnosed with *Toxoplasma* infection. There were also 2 preterm deliveries, mentioned before in the group of women with seizures. Half of the women with adverse outcome took folic acid periconceptionally.

Upon exclusion of one spontaneous abortion due to *Toxoplasma* infection and one elective termination of pregnancy, we recorded 1 spontaneous abortion and 2 preterm deliveries among 23 women with epilepsy. In this prospective surveillance, no congenital malformation was recorded in the group of 23 women on LTG monotherapy.

Discussion

Sociodemographic/reproductive data, pregnancy planning and folic acid intake

In 2003, we conducted a survey in 569 Croatian women with low risk pregnancies in order to assess

Table 4. Clinical parameters of neonates born to mothers with favorable outcome according to pregnancy planning and folic acid intake

	GW Mean	GW SD	BL (cm) Mean	BL SD	BW (g) Mean	BW SD
Favorable - not planned and FA not taken n=4	38.50	0.58	49.25	0.96	2892.50	378.71
Favorable - planned and FA taken n=13	38.84	0.69	50.92	1.38	3606.15	400.93
All favorable pregnancies n=17	38.76	0.66	50.53	1.46	3438.24	480.02

GW, gestational weeks; BL, birth length; BW, birth weight; FA, folic acid; SD, standard deviation

Table 5. Women with adverse pregnancy outcomes (N=6)

Patients with epilepsy N=6	AED before pregnancy mg/day	Max LTG during pregnancy mg/day	Max LTG after pregnancy mg/day	Pregnancy outcome	Pregnancy planning	Folic acid intake
1	LTG 175	175	175	Elective termination of pregnancy	No	No
2	CBZ + MPB	400	300	Preterm delivery, hypotrophic neonate	Yes	Yes
3	LTG 150	175	150	Preterm delivery, Apgar 7/8	No	Yes
4	LTG 25	100	100	Spontaneous abortion at 5 gestational weeks	No	No
5	VPA	150	150	Fetal intrauterine death	No	No
6	VPA	125	125	Spontaneous abortion at 7 gestational weeks (toxoplasmosis)	Yes	Yes

AED, antiepileptic drug; LTL, lamotrigine; CBZ, carbamazepine; MPB, methylphenobarbitone; VPA, valproic acid

the proportion of pregnancy planning in Croatia and periconceptional folic acid intake in low risk pregnancies[16]. Comparison of data on these women with low risk pregnancies and our women with epilepsy yielded a lower proportion of high level of education in women with epilepsy, whereas proportions in the values of marital status, family income, parity and previous spontaneous abortions were the same. Half of the women with epilepsy planned their pregnancy compared to 75% of planned low risk pregnancies in Croatia, but even 16/23 of women with epilepsy took folic acid properly compared to only 14% of women with low risk pregnancies. Gjergja *et al.* found statistical significance for higher educational level and family income with folic acid awareness and intake[16]. In this group of women with epilepsy proper preconception counseling was crucial for the high proportion of periconceptional folic acid intake. They had received counseling about the benefits of long-term folic acid supplementation in case of AED therapy. The effect of the addition of folic acid to LTG therapy was investigated by Ali *et al.*[17]. They concluded that the combination of LTG and folic acid significantly reduced depression, while enhancing the effects on memory and seizure threshold at the same time. LTG does not affect the seizure and memory threshold. LTG is a dihydrofolate reductase inhibitor, and it decreases fetal folate levels in rats. Nevertheless, while LTG therapy has not been associated with significant changes in serum folate, periconceptional folic acid supplementation is recommended[18].

In their case-control study, Palma *et al.* found no correlation between folic acid only (15 mg/day) and low birth weight (LBW), whereas iron supplementation (80 mg ferrous sulfate) was associated with a lower risk of LBW (odds ratio (OR) 0.58, 95% CI 0.34-0.98), adjusted for smoking, maternal education, body mass index, obstetric diseases during pregnancy, weight gain during pregnancy, and previous LBW[19]. Neither vitamin B12 nor folate concentrations in all three trimesters showed any significant associations with birth weight in a study by Takimoto *et al.*[20].

Newborns in our study had very significantly higher values of BW in the group of mothers with epilepsy, planned pregnancy and folic acid intake. Because of the small sample size and no adequate power of statistical analysis, we can only assume that the better pre/pregnancy care, pregnancy planning and folic acid intake influenced better results in anthropometric measures of newborns in our study. As this was a prospective study and only a part of a bigger prospective surveillance in Croatian pregnant women with epilepsy, we will draw final conclusions after getting larger sample size and control group.

Drug monitoring during pregnancy

The mechanisms of action of LTG have not yet been full understood and there are few hypotheses:

from the possibility that LTG inhibits synaptic release of glutamate by acting on Na+ channels[21], to interfere with neuronal sodium channels and inhibit the release of excitatory amino acids, glutamate and aspartate[22], or to decrease glutamate release[23]. LTG is metabolized primarily by glucuronidation.

Today, neurologists rely on clinical parameters and on monitoring drug concentration in plasma in order to administer an LTG dosage that would be within the therapeutic limits. Obviously, it is not always easy to achieve in pregnant patients. Petrenaite *et al.* retrospectively reviewed 11 pregnant women on LTG monotherapy and observed a significant decrease in the plasma LTG concentration-to-dose ratio (65.1%) during second trimester (P=0.0058); it was followed by a 65.8% decrease during third trimester (P=0.0045) compared to pre-pregnancy values. Five patients experienced seizure deterioration during pregnancy. The pharmacokinetic changes displayed inter-patient variation[24]. In our group of women, there was also marked inter-patient variation, stressing the need of evaluating each woman individually by closely monitoring LTG concentrations until full term and at least 8 weeks afterwards. Harden concludes that LTG levels can be expected to decline by 65%-90% during pregnancy[25].

Patients should be monitored carefully during pregnancy, both clinically and by serum levels. De Haan *et al.* also suggest that frequent LTG level monitoring and appropriate dose adjustments are advised in the periods before and during pregnancy, as well as after delivery, especially in women on LTG monotherapy[26]. Frequent LTG dose readjustments in our study demanded full women's compliance and cooperation. Adab suggests that changes in LTG clearance are particularly marked, with increases in each trimester and a significant fall in plasma concentrations, leading to subsequent breakthrough seizures in some women[27]. From our experience, there is no way to know which woman will have seizures and in which period of pregnancy, even by frequent measuring plasma LTG concentrations. Out of 15 our women that needed LTG adjustment, 8 had seizure deterioration during pregnancy. LTG concentrations may also rise after delivery, leading to symptoms of toxicity[28]. Regular drug monitoring has been advocated in each trimester and shortly after delivery, with appropriate adjustment of dosage to avoid seizure precipitation during pregnancy or symptoms of toxicity after delivery. Frequent monitoring has been recommended for LTG[29]. We suggest that the frequency of drug monitoring should also be individually adjusted to each woman. Some of our women needed drug monitoring every week because of seizures and frequent changes in LTG concentrations, whereas some others were monitored once in each trimester. In our surveillance we wanted to put emphasis not on plasma LTG concentrations, but on the mean and maximal doses in women with epilepsy, in order to point to the clinician how high the LTG dose should be to have the plasma LTG concentration within the therapeutic range.

In our series of pregnant women, there was no effect of dose, up to 400 mg/day, on the adverse outcome of pregnancy. The same has been reported by Cunnington *et al.* who analyzed data from the International Lamotrigine Pregnancy Registry in order to examine the effect of maximal first-trimester maternal dose of LTG monotherapy on the risk of major birth defects. The distribution of dose did not differ between infants with and those without birth defects. A logistic regression analysis showed no difference in the risk of MBDs as a continuous function of dose. There was no effect of dose, up to 400 mg/day, on the frequency of birth defects either[28].

Data from human studies indicate that LTG crosses the placenta. Ohman *et al.* report on a decrease in plasma level of LTG as pregnancy progressed[29]. The dose to plasma concentration ratio was 5.8 times higher at delivery and 3.6 times higher in late pregnancy. Castel-Branco *et al.* report that LTG plasma levels may be good indicators of LTG levels in the brain, and that higher response intensities could be expected with higher doses of LTG, since efficacious concentrations are maintained for a longer period[30]. Johannessen and Tomson suggest that, for the newer AEDs that are metabolized (felbamate, LTG, oxcarbazepine, tiagabine and zonisamide), pharmacokinetic variability is just as relevant as for many of the older AEDs. Therefore, therapeutic drug monitoring is likely to be useful in many clinical settings for the newer AEDs[31].

Clinicians involved in antiepileptic therapy of pregnant women should be aware of inter-individual differences in the kinetics of LTG among pregnant women. This variability is considered to be the conse-

quence of other drug intake, age, body habitus, smoking, comorbidity, etc. Recently, the genetic polymorphism of UDP glucuronosyltransferase 1A (UGT1A) is considered to be one of the main reasons for individual diversity of LTG kinetics during pregnancy[13,24,25]. The proportions of higher clearance of LTG during pregnancy are very likely a reflection of the specific metabolic pathway of LTG, glucuronidation and influence of steroids from the ovary. Ohman *et al.* analyzed LTG metabolites during pregnancy and found an increased 2N glucuronide/lamotrigine ratio during pregnancy. It points to the increased metabolism of LTG because of glucuronidation[32]. Additional research into the impact of pregnancy on LTG metabolism is necessary, along with further study of the pharmacokinetics and pharmacodynamics of LTG in pregnancy.

If the woman with epilepsy is treated with a potentially teratogenic AED, it is desirable to switch it to LTG or some other AED before planned pregnancy. Our group of seven women with therapy switch 10 days to 1 month before index pregnancy had 2 adverse outcomes: one fetal intrauterine death and one preterm delivery. Considering these results, it would be wise to wait with pregnancy for at least 2 months after therapy switch. In the group of women with favorable outcome, 4 had AED therapy switch to LTG, but more than 6 months before the index pregnancy.

Conclusion

Croatian pregnant women with epilepsy on LTG monotherapy demonstrated high awareness of pregnancy planning and folic acid intake. Considering our series of women with epilepsy, LTG can be the AED of choice in epilepsy treatment during pregnancy. Classic AED could be replaced with LTG even during pregnancy if we evaluate the same efficacy in epilepsy treatment with lesser teratogenic risk. Individual approach to the woman with epilepsy and monotherapy with minimal efficacious LTG dose with frequent drug monitoring enlarges the possibility of successful pregnancy. Taking into account all the possible risks and complications during pregnancy in women with epilepsy, the management of these women should begin with pre-pregnancy counseling. Preconception counseling and coordination among all members of the health care team is a key to successful surveillance of women with epilepsy of reproductive age. Planned pregnancy enables proper periconceptional folic acid supplementation and increases the likelihood of favorable outcome in women with epilepsy. No teratogenicity was observed in this series of pregnancies. Further follow up of their live births till school age will be provided by neuropediatricians in order to assess the potential long-term neurodevelopmental effect of AED on the offspring.

Despite the small number of cases in the study, these data indicate that treatment with LTG during pregnancy might be relatively safe. Larger prospective studies are needed to obtain adequate power for statistical analysis including large long-term cohort studies.

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Sažetak

PROSPEKTIVNO PRAĆENJE TRUDNICA NA MONOTERAPIJI LAMOTRIGINOM U HRVATSKOJ – PREDKONCEPCIJSKO SAVJETOVANJE I PRAĆENJE LIJEKOVA

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U ovoj studiji smo prospektivno pratili ishod trudnoće u 23 trudnice s epilepsijom koje su uzimale lamotrigin kao monoterapiju. Trudnoća je kod bolesnica rezultirala intrauterinom smrću djeteta u jednom slučaju, spontanim abortusom u jednom slučaju, te prijevremenim porodom u dva slučaja. Kod novorođenčadi nisu zabilježene kongenitalne malformacije. Žene koje su planirale trudnoću i uzimale folnu kiselinu rodile su djecu s višom tjelesnom masom i visinom. Postojala je velika različitost među bolesnicama u praćenju doze lijeka te u potrebi za usklađivanjem doze. Veća je mogućnost uspješnog planiranja trudnoće ako se svakoj bolesnici pristupi individualno uz minimalnu djelotvornu dozu lijeka (lamotrigin). Liječenje trudnica treba započeti savjetovanjem prije začeća kada je moguće i pravodobno započeti s uzimanjem folne kiseline. Unatoč malom broju slučajeva podaci iz naše studije pokazuju kako liječenje lamotriginom tijekom trudnoće može biti relativno sigurno. Potrebne su veće prospektivne studije kako bi se postigla zadovoljavajuća statistička snaga dobivenih podataka.

Ključne riječi: *Trudnoća – komplikacije; Trudnoća – terapija lijekovima; Epilepsija – terapija lijekovima; Epilepsija – metabolizam; Antikonvulzivi – krv*