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# THE CROATIAN MODEL OF INTEGRATIVE PROSPECTIVE MANAGEMENT OF EPILEPSY AND PREGNANCY

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SUMMARY – Epilepsy is the most common neurological complication in pregnancy. Women with epilepsy have a higher risk of complications in pregnancy. In Croatia, women with epilepsy are treated by neurologists at tertiary centers according to the place of residence. We prospectively followed-up pregnancies in women with epilepsy and healthy controls, and analyzed the factors responsible for their delivery outcomes and development of their babies. Healthy pregnant women had a higher level of education and economic status, but pregnant women with epilepsy took folic acid in a higher proportion than controls, possibly due to timely preconception counseling. Complications during pregnancy depended on the number of antiepileptic drugs and epilepsy control. We noticed some behavioral and cognitive aspects in children exposed *in utero* to valproic acid, which required follow up. The rate of congenital malformations was not increased. In conclusion, women with epilepsy should receive preconception counseling about the risk for pregnancy, but also about the possibilities to minimize that risk. We have introduced a model of integrative management of pregnancy and epilepsy based on close collaboration among different clinical experts in Croatia, in order to provide prompt counseling and timely intervention.

Key words: *Epilepsy; Pregnancy; Antiepileptic drugs; Seizures; Congenital malformations*

## Introduction

About 50 million people worldwide suffer from epilepsy, including women of fertile age. Epilepsy is the most common neurological complication in pregnancy. Women with epilepsy have a higher risk of complications in pregnancy as compared with healthy ones, e.g., the risk of hyperemesis gravidarum is almost twofold, preterm pregnancy threefold, hypertension in pregnancy-preeclampsia almost twofold, cesarean section and placental rupture twofold to threefold, and perinatal mortality up to eight times greater[1]. Considering that 0.3%-0.6% of all pregnant women have epilepsy and therefore 1 of 250 embryos/fetuses is exposed to antiepileptic drugs (AEDs), it is worth efforts of health professionals to try to improve the quality of management in such pregnancies[2].

In general population, there is a 3%-4% risk of having a child with major congenital anomaly. About 10% of these anomalies can be attributed to maternal drug intake, exposure to chemical substances, infections, or familial disease. Pregnant women with epilepsy are at

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a higher risk of unfavorable outcome of pregnancy because of taking different types of AEDs as potential teratogens, the possibility of epileptic seizure impairment, genetic factors, and comorbidities[2-4]. Adverse AED effects on the embryo or fetus can present as fetal loss, intrauterine growth retardation (IUGR), congenital malformations, impaired postnatal development, and behavior problems.

Despite efforts invested so far, some risk factors for unfavorable obstetric outcomes in women with epilepsy remain inadequately understood. Complex metabolic and excretion interactions between the mother and the fetus in case of epilepsy are misbalanced due to the impact of AED on sex steroid levels and possible other disturbances of maternal homeostasis. There are no sufficient studies of the impact of AED on the level of steroid hormones and non-steroids during pregnancy, delivery and puerperal period. Bag *et al*. compared the sex steroid hormone levels during pregnancy between the groups with increased and not increased seizure frequency. The increased seizure group had significantly higher estrogen levels, lower levels of progesterone, and lower levels of AEDs. In addition, the authors noted that patients having had abortions and those having developed epileptic status had high serum estrogen levels[5]. Falling serum levels of progesterone may be associated with increased seizure frequency, and may be most prevalent around parturition[6].

There is a higher risk of adverse effects in such pregnancies regardless of AED therapy, but it is mostly connected with AED intake. The risk is higher in longer duration and treatment of epilepsy. In pregnant women on monotherapy, the risk is 2.9% for lamotrigine (LTG), carbamazepine (CBZ) and oxcarbazepine (OXC) to 7.2% for valproic acid (VPA)[2,7,8]. The risk is twice higher with the intake of 2 or more AEDs or with high AED concentration in plasma. The incidence of malformations in children is highest (12.7%) in women taking more AEDs and having seizures during pregnancy[2,7,8]. Preconception counseling is the process of planning and preparing for pregnancy and gaining optimal balance of physical, emotional and mental health before conception. In women with epilepsy, preparing for pregnancy includes analysis of previous antiepileptic treatment in order to minimize the risk factors for both the fetus and the mother.

Patients with epilepsy in Croatia are usually treated in tertiary level centers by subspecialists (neurologists and pediatric neurologists) and women with epilepsy are referred by their primary care physicians to hospital according to the place of residence. Primary care practitioners follow the instructions from tertiary level specialists without active involvement in therapy switch. According to this issue, the greatest responsibility is on the neurologist, who must be timely informed about the possible pregnancy in order to adjust patient therapy.

## Material and Methods

This article describes prospective surveillance of pregnant women with epilepsy from May 2003 till May 2013 at the Sestre milosrdnice University Hospital Center in Zagreb, Croatia. All data were obtained from women with epilepsy and their documentation during outpatient visits to the neurologist, gynecologist and pediatrician neurologist. Data collected on pregnant women included age, socio-demographic data (marital status, income and education), smoking habit, previous loss of pregnancy or children, parity, actual pregnancy planning, type of epilepsy, electroencephalography (EEG) findings, AED dosage before and during pregnancy, actual pregnancy data (folic acid intake, vitamin K, seizures during pregnancy, ultrasound (US) findings and complications). Prenatal US and other relevant prenatal testing was performed as requested by the gynecologist or pediatrician/geneticist (triple test, amniocentesis, etc.). Newborns were examined by pediatrician neurologist/geneticist at Clinical Department of Pediatrics and followed up yearly till school age. Data on newborns/children included term/mode of delivery, Apgar score, body weight, body height, and early psychomotor development. Results were compared with those in healthy control subjects. Detailed examination of the newborn included anthropometric measurements, clinical features, if relevant, photos of dysmorphic features, search for minor and major anomalies, and yearly evaluation of neurological development. When needed, psychological testing was performed including evaluation of intellectual capacities in older children (Kohs, numeric factor, social functioning, dictionary, perceptive motor skills, motor velocity as measure of concentration, attention span, Bender gestalt, etc.). All newborns underwent screening for hearing. Other findings were also included if needed (brain US, ECHO, abdominal

US, karyotyping, brain computed tomography (CT) or magnetic resonance imaging (MRI), vision, etc.).

Data on the control group were obtained from Clinical Department of Gynecology and Obstetrics and included age, socio-demographic data (marital status, income and education), pregnancy planning, smoking habit, previous loss of pregnancy or children, parity, actual pregnancy planning, actual pregnancy data (folic acid intake, vitamin K, US findings, complications and pregnancy outcome). Mothers with chronic diseases and smokers were excluded from the study. Data on newborns from the control group were collected prospectively from Clinical Department of Gynecology and Obstetrics and Clinical Department of Pediatrics and included delivery term and mode, Apgar score, body weight and body height. Examination of the newborns included anthropometric measurements, clinical features, search for minor and major anomalies, and neurological evaluation.

### *Statistics*

Statistical analysis was performed in Microsoft Office Excel 2010 program using XLSTAT add-on (ver. 2011.5.01). Results were presented in tables or graphs, showing descriptive statistics parameters (mean, standard deviation and percentage). Mean values of maternal and neonatal conditions and pregnancy outcomes were compared using the unpaired Student's t-test for numeric variables with normally distributed values and Kolmogorov-Smirnov two-tailed test if otherwise. Distributions of categorical and ordinal variables were compared using the $\chi^2$-test. The values of $p \leq 0.05$ were considered statistically significant.

### *Standard protocol approvals, registrations and patient consents*

The researchers contacted all women included and obtained their written consent prior to inclusion in the study. The study was approved by the Ethics Board of the Sestre milosrdnice University Hospital Center in Zagreb, and was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

## Results

During the period from May 2003 till May 2013, we prospectively followed-up 74 pregnancies in women with epilepsy (group 1) and 147 healthy controls (group 2). The average age was 34 (22-39) years in group 1 and 36 (19-49) years in group 2 ($p>0.05$).

### *Socio-demographic status*

Socio-demographic status of the two groups of pregnant women is shown in Table 1. Healthy pregnant women had a significantly higher level of education and economic status, whereas there was no between-group difference according to marital status (Table 1).

### *Smoking*

The association of smoking and delivery outcome (premature delivery and spontaneous abortion) was evident in the group of women with epilepsy. There were six smokers, of which three had early spontaneous abortions and one had premature delivery at 36 weeks + 5 days. Control group of healthy women were non-smokers during pregnancy and there was no case of spontaneous abortion in this group.

### *Folic acid intake and preconception counseling of epileptic women*

Healthy controls planned their pregnancy in a significantly higher number of pregnancies (114/128 or 89.06%) as compared to 35% (26/74) of women with epilepsy (Table 1). About 60% of pregnant women with epilepsy had received preconception counseling as compared to none in the control group and about 20% of women with epilepsy took folic acid (FA) properly, as compared to only 2.7% in the control group (Table 1). Even more, pregnant women with epilepsy having attended preconception counseling had significantly less spontaneous abortions and stillbirths as compared to those not having received preconception counseling (Fig. 1).

### *Antiepileptic therapy*

Monitored women with epilepsy during pregnancy were prescribed different types of AED: LTG, VPA, phenytoin (PHT), phenobarbitone (PB), gabapentin (GBP), topiramate (TPM), CBZ, clonazepam (CZP), and OXC. In 62 of 70 (88.6%) monitored pregnancies, women were on monotherapy: mostly (37/62) on LTG, 13/62 on CBZ, 6 on VPA, 3 on PB, 1 on OXC, 2 on GBP, and 1 on PHT. Eight pregnancies (8/70 or

*Table 1. Socio-demographic data on pregnancy planning and folic acid intake in two groups of pregnant women*

| | Group 1 Epilepsy | Group 2 Control | Kolmogorov-Smirnov test /two-tailed test |
|---|---|---|---|
| **Income** | | | |
| Above average | 3 | 9 | D=0.104, p=0.038, α=0.05 |
| Average | 62 | 98 | |
| Below average | 5 | 21 | |
| Missing value | 4 | 0 | |
| **Marital status** | | | |
| Married | 60 | 124 | D=0.026, p=0.489, α=0.05 |
| Single | 5 | 2 | |
| Divorced | 5 | 2 | |
| Widow | 0 | 0 | |
| Missing value | 4 | 0 | |
| **Education** | | | |
| University | 6 | 37 | D=0.405, p<0.0001, α=0.05 |
| Secondary school | 43 | 79 | |
| Elementary school | 24 | 12 | |
| Missing value | 2 | 0 | |
| **Smoking** | | | |
| Yes | 6 | 31 | D=0.203, p<0.0001, α=0.05 |
| No | 49 | 97 | |
| Missing value | 10 | 0 | |
| **Pregnancy planning** | | | |
| Yes | 26 | 114 | D=0.332, p<0.0001, α=0.05 |
| No | 47 | 14 | |
| Missing value | 1 | 0 | |
| **Pre-pregnancy counseling** | | | |
| Yes | 44 | 0 | D=1.000, p<0.0001, α=0.05 |
| No | 25 | 128 | |
| Missing value | 5 | 0 | |
| **Folic acid intake** | | | |
| Yes | 37 | 4 | D=0.530, p<0.0001, α=0.05 |
| No | 17 | 124 | |
| Only during pregnancy | 11 | 0 | |
| Missing value | 9 | 0 | |

11.4%) were on polytherapy with the following combinations: TPM/VP, LTG/CBZ, CBZ/PB, TPM/CBZ/PHT and VP/CZP. Four pregnant women were without AEDs.

*Seizures*

About 40% of women with epilepsy in our study had seizures during pregnancy. A higher proportion of women on polytherapy (63%) had seizures during pregnancy as compared to those on monotherapy (37%) (Table 2). None had status epilepticus during pregnancy. There was no difference in the mode of delivery (vaginal or cesarean section) between the groups with epilepsy and healthy controls, but women with seizures during pregnancy delivered with cesarean section more frequently than those without seizures. The AED dosage had to be increased in 53% of pregnancies (50% on monotherapy and 75% on polytherapy) and to switch AED in 26% of pregnancies (23% on monotherapy and 50% on polytherapy) (Table 2).

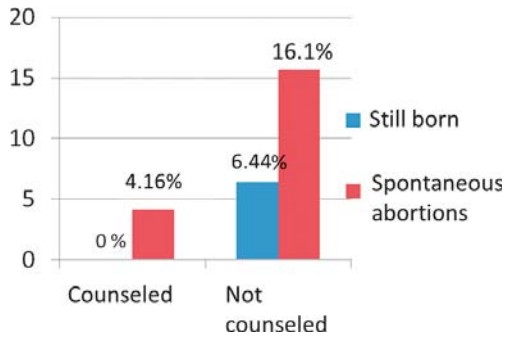


*Fig. 1. Differences between pregnant women with epilepsy having and not having attended preconception counseling ($\chi$=18.45; DF 1; p<0.05).*

### *Mode of delivery and anthropometric measurements of neonates*

When we cut out women with early spontaneous abortions in the epileptic group, there was no statistical difference in the mode of delivery between the control and epileptic women. In each group, 25% of women had cesarean section performed (25% or 36/147 *vs.* 25% or 16/64). There were no statistical differences in neonatal birth length or birth weight between the women with epilepsy and healthy controls, except for the group under 500 g, due to stillbirths/spontaneous abortions in mothers with epilepsy. The neonates of healthy controls had a significantly better Apgar score (p=0.004; D=0.205) (Table 3).

### *Adverse effects on embryo or fetus*

Healthy controls had a significantly lower number of complications in pregnancy (p<0.0001; D=0.246). Furthermore, when we compared women with epilepsy according to the number of AEDs, about 40% of pregnancies on AED polytherapy resulted in various complications as compared to 20% of pregnancies on AED monotherapy (Table 4). Moreover, monitoring of pregnancies on monotherapy with VPA and CBZ revealed that AED polytherapy involving VPA and CBZ with different AEDs resulted in a larger proportion of complications and adverse outcomes as compared to monotherapy with those AEDs (Table 4).

### *Fetal loss*

Fetal loss occurred in 9/74 followed-up pregnancies in women with epilepsy. It was due to intrauterine death, spontaneous abortion, or stillbirth. In comparison to the control group, there was a significantly higher number of spontaneous abortions in women with epilepsy (p=0.001; D=0.081). Artificial abortion is legal in Croatia until 10$^{th}$ week of gestation and one woman with epilepsy on LTG therapy decided to terminate pregnancy before 10 weeks of gestation for fear from adverse effects in pregnancy.

### *Intrauterine growth retardation (IUGR)*

In our study, 2 live births were surveyed prenatally because of IUGR. The first one was exposed to CBZ/

*Table 2. Antiepileptic therapy in 70 pregnancies according to monotherapy and polytherapy*

| | Total | Monotherapy | Polytherapy |
|---|---|---|---|
| Number of pregnancies on AET | 70 | 62 (88.6%) | 8 (11.4%) |
| Seizures in pregnancy | | | |
| Yes | 28/70 (40%) | 23/62 (37.1%) | 5/8 (62.5%) |
| No | 42/70 (60%) | 39/62 (62.9%) | 3/8 (37.5%) |
| Number of pregnancy | | | |
| 1 | 53/70 (75.7%) | 47/62 (75.8%) | 6/8 (75.0%) |
| 2 | 15/70 (21.4%) | 14/62 (22.6%) | 1/8 (12.5%) |
| 3 | 2/70 (2.9 %) | 1/62 (1.6%) | 1/8 (12.5%) |
| AET dose increase in pregnancy | | | |
| No | 33/70 (47.1%) | 31/62 (50%) | 2/8 (25%) |
| Yes | 37/70 (52.9%) | 31/62 (50 %) | 6/8 (75%) |
| AET change in pregnancy | | | |
| No | 52/70 (74.3%) | 48/62 (77.4%) | 4/8 (50%) |
| Yes | 18/70 (25.7%) | 14/62 (22.6%) | 4/8 (50%) |

AET = antiepileptic therapy

*Table 3. Pregnancy outcomes in two groups of pregnant women*

| | Group 1 Epilepsy | Group 2 Controls | Kolmogorov-Smirnov two-tailed test |
|---|---|---|---|
| **Mode of delivery** | | | |
| Vaginal | 44 (63.8%) | 92 (71.9%) | Nonsignificant |
| Cesarean section | 15 (21.7%) | 36 (28.1%) | Nonsignificant |
| Missing data | 5 | 0 | |
| **Pregnancy outcome** | | | |
| 0 preterm LB | 5 (6.8%) | 4 (3%) | D=0.006, p=1.000 |
| 1 term LB | 59 (79.7%) | 124 (97%) | Nonsignificant |
| 2 SB | 2 (2.7%) | 0 | D=0.027, p=0.111 |
| 3 SA | 7 (9.5%) | 0 | D=0.081, p=0.001 |
| 4 med. induced abortion | 0 | 0 | Nonsignificant |
| 5 artificial abortion | 1 (1.4%) | 0 | |
| **Weight at delivery/abortion** | | | |
| 0-499 g | 10 (13.5%) | 0 | D=0.205, p=0.004 |
| 500-1499 g | 1 (1.4%) | 0 | Nonsignificant |
| 1500-2499 g | 5 (6.7%) | 2 (1.6%) | Nonsignificant |
| 2500-2999 g | 12 (16.2%) | 31 (24.2%) | Nonsignificant |
| 3000-3999 g | 42 (56.8%) | 93 (72.6%) | Nonsignificant |
| 4000-4500 g | 4 (5.4%) | 2 (1.6%) | Nonsignificant |
| **Length at delivery/abortion** | | | |
| 0-38 cm | 12 (16.2%) | 0 | D=0.082, p=0.003 |
| 39-49 cm | 21 (28.4%) | 39 (30.5%) | Nonsignificant |
| 50-55 cm | 41 (55.4%) | 89 (69.5%) | Nonsignificant |
| **First Apgar score** | | | |
| 0-1 | 10 (13.4%) | 0 | D=0.205, p=0.004 |
| 5-7 | 4 (5.4%) | 15 (11.7%) | alpha=0.05 |
| 8-10 | 60 (81.2%) | 113 (88.3%) | |
| **Congenital anomalies** | | | |
| Yes | 2 (2.7%) | 0 | D=0.063, p=0.005, |
| No | 72 (97.3%) | 128 | alpha=0.05 |
| **Hyperemesis gravidarum** | | | |
| Yes | 4 (5.4%) | 5 (3.9%) | D=0.068, p=0.004, |
| No | 70 (94.6%) | 123 (96.1%) | alpha=0.05 |
| **Preeclampsia** | | | |
| Yes | 4 (5.4%) | 2 (1.6%) | Nonsignificant |
| No | 70 (94.6%) | 126 (98.4%) | Nonsignificant |

LB = live birth; SB = stillbirth; SA = spontaneous abortion

TPM/PHT and during follow up remained with short stature and facial features indicative of the possible fetal anticonvulsant effect (Fig. 2A and B), but had normal psychomotor development. The other one was exposed prenatally to GBP. He had atrial septal defect discovered after birth and delayed psychomotor development. He suffers from intractable myoclonic epilepsy since infancy. The extensive work-up excluded chromosomal aberration and inherited metabolic disorder, and no specific syndrome was revealed by the geneticist.

### *Major congenital malformations, pervasive and behavioral aspects, and cognitive abilities*

Out of 74 prospectively followed-up pregnancies with epilepsy, one child (1/74 or 1.4%) prenatally exposed to GBP had congenital heart defect (atrial septal defect), while no congenital anomalies at birth were

*Table 4. Outcomes of pregnancies according to antiepileptic therapy*

| |
|---|
| **62 pregnancies on monotherapy:**<br>LTG: 26 LB, 2 premature deliveries, 3 SA, 1 artificial abortion, 1 intrauterine death<br>CBZ: 11 LB and 2 SA<br>PHT: 1 LB<br>PB: 1 SA and 2 LB<br>GBP: 1 LB and 1 preterm LB with ASD, psychomotor delay and epilepsy<br>VPA: 6 LB<br>OXC: 2 LB |
| **8 pregnancies on polytherapy:**<br>VPA/TPM: 2 LB, 1 SA<br>VPA/CZP: 1 LB<br>CBZ/PB: 1 SB<br>CBZ/TPM /PHT: 1 LB with IUGR and facial dysmorphism<br>CBZ/PHT: 1 LB<br>LTG/CBZ 1 LB |
| **4 pregnancies without AED**:<br>All 4 LB |

LB = live birth; SB = stillbirth; SA = spontaneous abortion; LTG = lamotrigine; CBZ = carbamazepine; PHT = phenytoin; PB = phenobarbitone; GBP = gabapentin; VPA = valproic acid; OXC = oxcarbazepine; TPM = topiramate; CZP = clonazepam; ASD = atrial septal defect; IUGR = intrauterine growth retardation

observed in control group (p=0.005, D=0.063). The above mentioned child exposed to polytherapy with CBZ/TPM/PHT, with IUGR, born on term from the fourth pregnancy, had dysmorphic facial features in accordance with fetal anticonvulsant effect (Fig. 2). He was prospectively followed-up till school age, his psychomotor development is normal and he has no congenital malformations. Two boys, one exposed to LTG and other one to VPA, had the spectrum of attention deficit hyperactivity disorder. The boy exposed to LTG had behavioral disturbances accompanied with aggression, stubbornness and learning difficulties. One girl, exposed *in utero* to VPA had attention deficit hyperactivity disorder, and slight psychomotor and speech developmental delay. Her mother had one spontaneous abortion from pregnancy on VPA and TPM. All three children were prospectively followed-up, and they all had one-year delay in starting school due to difficulties in fine motor skills, expressive language skills and attention deficit, and hyperactivity. We had no children with clear evidence for autistic spectrum disorder, especially regarding the group of children prenatally exposed to VPA.

*Fig. 2A and B. The boy with short stature and craniofacial dysmorphism, prenatally exposed to polytherapy with carbamazepine/topiramate/phenytoin (with permission of parents).*

## Discussion

### *Socioeconomic status of epileptic pregnant women*

In the current study, healthy pregnant women had significantly better levels of education and economic

status. According to previous reports, financial issue is a major problem for patients with epilepsy[9]. The longer the duration of epilepsy, the worse the psychological issues are[10,11]. Epileptic patients have poor education and achievement later in life[10]. Patients who have epilepsy at school age have worse learning achievement[10]. Campbell *et al*. observed no difference in the rate of major congenital anomalies between the groups of women with low income and education and those with higher income and education[12]. Less deprived women were more likely to take preconception FA and less likely to have generalized tonic-clonic seizures in pregnancy than socially deprived ones. They also were more likely to be on monotherapy, less likely to be on VPA, and more likely to be on lower doses of the drug compared to socially deprived ones[12]. As differences in treatment between socioeconomic groups do exist, particularly in preconception FA consumption, AED choice and seizure frequency, there should be benefit from preconception counseling for women with low socioeconomic status, to discuss AED choice and FA intake and to improve chances for normal pregnancy and delivery.

### *Smoking*

Lower birth weight of newborns of all gestational ages was observed in teenage and adult mothers with epilepsy who smoked[13], as well as negative effect of maternal smoking on fetal growth[14]. Our data on 24% of pregnant women smoking during pregnancy in Croatia are more or less consistent with the recently published data on 50% of Croatian pregnant women having smoked before pregnancy and 19% continuing smoking during pregnancy[15]. It has already been proposed that women with epilepsy who smoke be warned that they possibly are at a substantially higher risk of premature contractions and premature labor and delivery[16], and we promote this attitude during counseling of women with epilepsy in Croatia. In the group of women with epilepsy, there was strong association of smoking and early spontaneous abortions; these women did not take FA during pregnancy, one-third of them had seizures during pregnancy, and it was difficult to observe only smoking as a variable because of the small number of women. The lower proportion of smokers in the group of women with epilepsy despite lower socioeconomic status as compared to healthy women could also be the result of our continuous counseling about epilepsy and pregnancy.

### *Folic acid intake and counseling of epileptic pregnant women*

As the majority of AEDs antagonize folate action, children born to women taking antiepileptic therapy are at an increased risk of birth defects. Thus, it is suggested that women with epilepsy take FA supplementation, especially in case of VPA therapy[17]. Pittschieler *et al*. analyzed 388 pregnancies in 244 patients and pregnancies with FA supplementation showed significant reduction of spontaneous abortion. In the group of women taking VPA as monotherapy, supplementation of FA had significant benefit. Other examined monotherapies (CBZ, PHE, and PB) known to interfere with FA showed no significant results. This study confirmed the prophylactic effect of FA supplementation on spontaneous abortion and the fact that FA supplementation should be included in therapy of every pregnant epileptic woman, especially those treated with VPA[18]. In the NEAD study of children exposed *in ute*ro to AED, maternal periconceptional folate intake was associated with higher IQ of their children at the age of six, but the authors concluded that this finding should be interpreted with caution because periconceptional folate was one of several confounding variables, and was established by retrospective maternal interview in the study of neurodevelopmental effects of AEDs[19]. In our study, the women with epilepsy having received prenatal counseling planned their pregnancies in a higher proportion as compared to the women with epilepsy without prenatal counseling. Sample size in our study was too small to determine whether FA protects against birth defects, but our surveillance showed that the prenatally counseled women with epilepsy took FA in a higher proportion and had significantly less fetal losses and stillbirths. Due to the fact that our surveillance was prospective, we can argue that preconception counseling in women with epilepsy could have resulted in a higher proportion of proper FA intake in women with epilepsy, despite the higher proportion of planned pregnancies in control subjects.

### *Seizures*

Among pregnant women with epilepsy, the severity of the seizure disorder is in concordance with the increased risk of adverse fetal outcomes[20] as a consequence using higher AED doses and polytherapy. It has been reported that >5 convulsions during preg-

nancy reduced cognitive levels in newborns[21]. The effects of AEDs on the child's cognitive outcome cannot be explained only by the severity of the maternal seizure disorder, as assessed in the analysis for the NEAD study and additional research is suggested. The increased volume of distribution and the hepatic metabolism of AEDs, along with decreased compliance during pregnancy and self-initiative interruption of AED intake because of concerns about their effects on the fetus, lead to an increase in seizure frequency during pregnancy in women with epilepsy. Seizures in women with epilepsy are observed in as many as 17%-40% of pregnancies[22,23]. In our study, 40% of women with epilepsy had seizures during pregnancy, but owing to close drug monitoring, AED increase (especially LTG) or therapy switch we had no epileptic status and no significantly increased percentage of complications in women with seizures during pregnancy, except for the higher number of cesarean sections.

*Mode of delivery and anthropometric measurements*

About 5% to 25% of deliveries in Croatia end up with cesarean section, depending on the hospital level and pathology of the population served. The most frequent specific indications for cesarean section in Croatia are cesarean section in previous pregnancy, prolonged delivery, fetal dystocia, and cardiotocography findings that require emergency delivery. Since both of our groups included women followed-up at a tertiary center where there is usually a higher percentage of cesarean sections, the higher percentage recorded in our study is not surprising. Although we had no data on the specific reasons of cesarean section in every woman, the fact is also that cesarean section performed upon patient request has been increasing in Croatia and in nearby countries[24]. The higher risk of Apgar score <7 in deliveries of women with epilepsy was also noticed by some authors[25]. It was not possible to identify specific factors for lower Apgar score in this study, except for preterm deliveries also resulting in lower birth weight.

*Fetal loss*

Since pregnancy loss can occur very early in pregnancy, it is hard to estimate the true fetal loss in pregnant women. Nine fetal losses (9/74 or 11.4%) in the epileptic group in the current study (7 spontaneous abortions and 2 stillbirths) were higher than some previously published data[18,25]. Thomas *et al*. showed a higher rate among women with epilepsy (4%) than in controls (2%). The risk was higher in women on valproate (8%) than in those on other AEDs (1%-6%)[25]. Pittschieler *et al*. report results of a non-randomized, partly retrospective study with 10% of spontaneous abortions in women with epilepsy and a lower range of spontaneous abortion among those using FA supplementation[18]. Our results also suggested a significantly higher risk of spontaneous abortion in epileptic pregnancies as compared to controls. One important result was a significantly lower risk of spontaneous abortion in women with epilepsy having received preconception counseling. Women in this group also took FA in a higher percentage than non-counseled ones. The group of women with epilepsy had a significantly higher FA supplementation as compared to controls, despite the higher proportion of planned pregnancies in controls. We can only suppose that preconception counseling enabled higher FA intake in women with epilepsy and possibly influenced the reduced risk of fetal loss in their pregnancies. The fact that a large proportion of fetal loss in general population is associated with chromosomal abnormalities and many occur too early to be recognized makes it difficult to estimate the true incidence of fetal loss due to epilepsy/AED. Furthermore, there are no larger studies with consistent data on chromosomal aberrations in pregnancies of women with epilepsy[26,27]. We can assume that the significant difference in fetal loss between these two prospectively followed-up groups was in connection with epilepsy and its potential to cause complications during pregnancy.

*Intrauterine growth retardation*

There are some data that AEDs can influence fetal growth suggesting an increasing risk of small for gestational age newborns exposed to AED *in utero*[28]. Some studies have shown that CBZ and VPA as monotherapy during pregnancy reduce the mean body weight-adjusted head circumference and that AED polytherapy increases the rate of microcephaly. According to these studies, the possible significance for further development of the child is uncertain and should be explored[29,30]. In our study, two live births were surveyed prenatally because of IUGR. The first

one was exposed to CBZ/TPM/PHT and remained with short stature during follow up, but also with facial dysmorphism due to the fetal anticonvulsant effect (Fig. 2A and B). The second case of IUGR was exposed to GBP, with cardiac anomaly (atrial septal defect) discovered after birth, had delayed psychomotor development during follow up, and started to suffer from intractable myoclonic epilepsy in infancy. Karyotype was normal in both cases.

### *Congenital malformations, pervasive and behavioral aspects, and cognitive abilities*

The extensive metabolic and genetic work-up found no specific syndrome in the boy prenatally exposed to GBP with psychomotor and somatic delay, generalized epilepsy and congenital heart anomaly. GBP has no specific pattern of congenital anomalies and data support the safety of GBP use in pregnancy; however, the number of exposures to date is still small[31]. The rate of 2.7% of major congenital anomalies in our group of women with epilepsy was in accordance with the rate of major congenital malformations in general population, but it was still higher in the group of women with epilepsy as compared to healthy controls with no congenital malformations found at birth ($\chi^2$-test=9.514; DF=2; significance level p=0.0086; contingency coefficient 0.201).

The boy exposed prenatally to CBZ/TPM/PHT (Fig. 2A and B) was born from irregularly controlled pregnancy at another institution. The mother came to our institution in 16$^{th}$ week of pregnancy, when we excluded CBZ from therapy and she remained on TPM and PHT, seizure free during pregnancy. Characteristic dysmorphic features have been described so far with fetal exposure to phenytoin, valproate, and CBZ. Fetal phenytoin is said to be associated with hypertelorism, broad nasal bridge, short nose, and facial hirsutism, while fetal CBZ face includes epicanthic folds, short nose, long philtrum, and upward slanting palpebral fissures, as in our patient mentioned above[32-34]. Although distinctive phenotypes have been described for different anticonvulsants, there is an overlap in both facial dysmorphic features and malformations.

Fetal anticonvulsant syndromes also consist of behavioral phenotype[34]. Of the three children with attention deficit/hyperactivity disorder (ADHD) in our study, the boy exposed prenatally to LTG improved his social skills with time and he attends regular school, but the other two children prenatally exposed to VPA are still under surveillance, psychotherapy and rehabilitation. The recently published data implicate that prenatal exposure to valproate can be associated with autistic spectrum disorder in the offspring, even after adjusting for maternal epilepsy[35]. It is recommended that this important information be shared with women of childbearing potential within the counseling when discussing treatment options that include valproate[36,37]. Taking this into account, in our group of women on VPA treatment we also balanced against the treatment benefits for women requiring valproate for epilepsy control and made therapy switch where possible (Table 4).

According to the NEAD study, fetal VPA exposure has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age and the positive association of periconceptional folate with IQ was consistent with other recent studies[19]. In this study, the mother of the child with mental delay and mothers of children with ADHD did not take FA periconceptionally, nor did the mother of the boy with fetal anticonvulsant syndrome. Bromley *et al.* compared the prevalence of neurodevelopmental disorders diagnosed in 415 children exposed *in utero* to different AEDs, and autistic spectrum disorder was the most frequent diagnosis. No significant increase was found among children exposed to CBZ or LTG[38]. An accumulation of evidence so far demonstrates that the risks associated with prenatal sodium VPA exposure include an increased prevalence of neurodevelopmental disorders[39,40]. The European Medicines Agency (EMA) has strengthened warnings on the use of VPA in women and girls (EMA November 21, 2014). As these restrictions have been incorporated in the amended Summary of Product Characteristics (SmPC) and package leaflets in all EU member states, the Commission of European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN) have appointed the Task Force and published recommendations for clinical use of VPA in the treatment of girls and women with epilepsy in the context of these new restrictions[41]. These Task Force's recommendations include the following: 1) where possible, valproate should be avoided in women of childbearing potential; 2) the choice of treatment for girls and women of childbearing poten-

tial should be based on a shared decision between clinician and patient, and where appropriate, the patient's representatives. Discussions should include careful risk-benefit assessment of reasonable treatment options for the patient's seizure or epilepsy type; 3) for seizure (or epilepsy) types where valproate is the most effective treatment, the risks and benefits of valproate and other treatment alternatives should be discussed; 4) valproate should not be prescribed as a first-line treatment for focal epilepsy; 5) valproate may be offered as a first-line treatment for epilepsy syndromes where it is the most effective treatment, including idiopathic (genetic) generalized syndromes associated with tonic-clonic seizures; 6) valproate may be offered as a first-line treatment in situations where pregnancy is highly unlikely (e.g., significant intellectual or physical disability); and 7) women and girls taking valproate require regular follow-up for ongoing consideration of the most appropriate treatment regimen[41].

For newer AEDs, one multicenter, observational prospective cohort study conducted by our ENTIS colleagues in 2016 demonstrated a signal for an increased risk of major birth defects after first trimester exposure to pregabalin, but these results need confirmation through independent studies[42]. Newer data also suggest that lamotrigine and levetiracetam are associated with a relatively low risk for both anatomic and developmental adverse effects, although further studies are needed for these and other AEDs[43].

### *The model of management of epilepsy in pregnancy in Croatia*

Croatia is a south-eastern European country, with about 4,500,000 inhabitants. The incidence, prevalence and mortality of epilepsy vary across countries with different economies[44], and according to Bielen *et al.*, it is likely that the prevalence of active epilepsy in Croatia is between 4.8 and 5.5/1000[45]. In Croatia, neurologists and pediatric neurologists are usually taking care of the people with epilepsy and general practitioners follow their advice and proceed with drug prescriptions. The usual frequency of outpatient visits to tertiary centers is every 3-6 months, depending on the severity of epilepsy. Our clinical hospital center has the 3rd largest maternity hospital in the country, with 3200 deliveries *per* year. If we consider the previous fact that 1 of 250 embryos/fetuses are exposed to AED[1], we can expect about 13 newborns exposed *in utero* to AEDs in our maternity hospital each year. Our health professionals working in the maternity hospital frequently have some issues with pregnant women with epilepsy. In order to improve the quality of management in such pregnancies, we have developed close collaboration among different specialists (gynecologists, neurologists, neonatologists and pediatric neurologists/geneticists). This collaboration has resulted in a prospective registry of pregnant women with epilepsy dating from 2003, and in scientific collaboration with institutions such as the Institute for Medical Research and Occupational Health in Croatia. After formation of the Teratology Information Service at the Department of Pediatrics in 2004 (TIS Zagreb, since 2010 at Srebrnjak Children's Hospital) and the Center for Counseling for Epilepsy and Pregnancy at the Clinical Department of Neurology, Sestre milosrdnice University Hospital Center, Sestre milosrdnice, women with epilepsy can be prospectively followed-up, offered pre-pregnancy counseling at the proper time, prospectively follow-up their pregnancy and children, from the neonatal period till school age or after it if needed.

## Conclusion

Our model of the integrative management of pregnancy and epilepsy includes close collaboration among clinical experts in neurology, gynecology, pediatrics and primary health care professionals (Fig. 3). Every woman with epilepsy in generative age should receive preconception counseling. Women with epilepsy should be encouraged to attend pre-pregnancy counseling during their ordinary follow up visits, using tickets from their primary health professionals, or as an emergency expertise if needed. Pregnant woman with epilepsy has to be counseled about the risk that her disease can bring, but also about the possibilities to minimize the risk by appropriate treatment, good control of epilepsy, quality of nutrition, vitamin intake, screening for congenital anomalies, and careful surveillance of pregnancy and delivery. Women with epilepsy that smoke should be counseled that they possibly have a substantially increased risk of premature contractions and premature labor and delivery.

Planned pregnancy with periconceptional FA intake increases the possibility of favorable outcome of pregnancy in women with epilepsy. Monotherapy and the lowest possible dose of AED in pregnant women

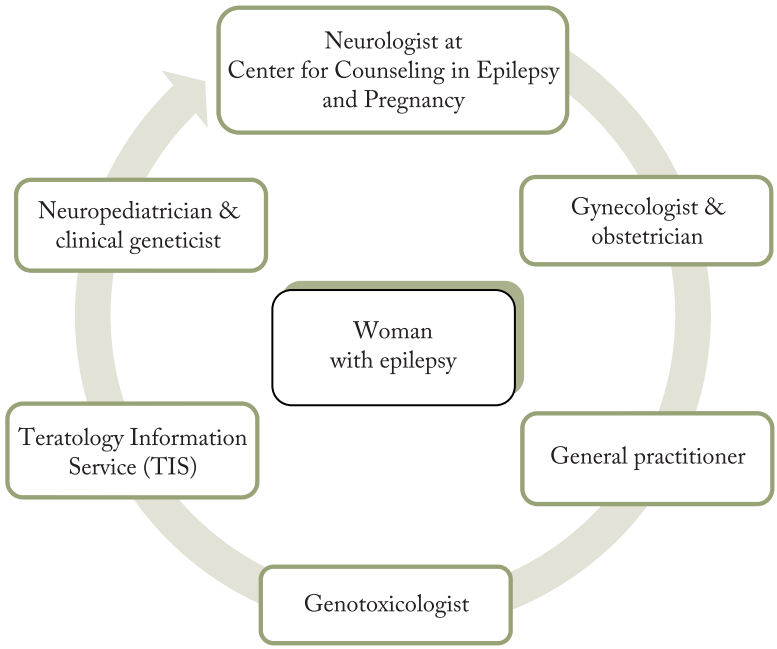


*Fig. 3. The model of integrative prospective management of epilepsy and pregnancy in Croatia.*

with epilepsy can lower the risk of congenital anomalies. Of newer AEDs, lamotrigine has the best documented data on the use in pregnancy. After being exposed to AED, no termination of pregnancy is indicated, but prenatal surveillance is needed as in other AED exposures, including alpha-fetoprotein screening and US examinations (anomaly scan). Frequent monitoring of LTG (and OXC) concentrations (at least monthly) is very helpful, with dose adjustment before, during and after pregnancy. Individual approach to every pregnant woman is advised because of inter-individual variations in pharmacokinetics.

Our study was limited by the small number of pregnancies on the same AED, but the intention of this study was not to analyze the effect of each AED on the fetus, but the benefits of the integrative model of pregnancy follow up in epilepsy.

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Sažetak

## HRVATSKI MODEL INTEGRATIVNE PROSPEKTIVNE SKRBI TRUDNOĆA U ŽENA S EPILEPSIJOM

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Epilepsija je najčešća neurološka komplikacija u trudnoći. Žene s epilepsijom imaju veći rizik za komplikacije u trudnoći. U Hrvatskoj žene s epilepsijom obično prate neurolozi u tercijarnim centrima prema mjestu njihova boravka. Mi smo prospektivno pratili trudnoće u žena s epilepsijom i u zdravih kontrolnih trudnica te analizirali čimbenike odgovorne za ishode trudnoća i razvoj njihove djece. Zdrave trudnice su imale višu razinu obrazovanja i ekonomskog statusa, ali su žene s epilepsijom uzimale folnu kiselinu u višem postotku nego zdrave trudnice zahvaljujući pravodobnom predkoncepcijskom savjetovanju. Komplikacije za vrijeme trudnoće ovisile su o broju antiepileptičnih lijekova i kontroli epilepsije. Zamijetili smo određene bihevijoralne i kognitivne aspekte u djece izložene *in utero* valproičnoj kiselini, što zahtijeva daljnje praćenje. Stopa kongenitalnih malformacija nije bila povišena. U zaključku, ženama s epilepsijom trebali bismo omogućiti predkoncepcijsko savjetovanje o rizicima u trudnoći, ali i o mogućnostima kako značajno smanjiti taj rizik. Predstavili smo model integrativne prospektivne skrbi trudnica s epilepsijom koji se temelji na bliskoj suradnji različitih kliničkih eksperata u Hrvatskoj, u cilju osiguranja promptnog savjetovanja i pravodobne intervencije.

Ključne riječi: *Epilepsija; Trudnoća; Antiepileptici; Epileptični napadaji; Kongenitalne malformacije*