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Scientific Research

Problems of Rational Therapy for Epilepsy during Pregnancy

Diana V. Dmitrenko*, Natalia A. Shnayder, Ilia A. Kiselev, Andrej V. Shulmin, Natalia V. Zhirova, Evgeniya A. Shapovalova, Elena A. Kantimirova, Elena N. Bochanova, Olga F. Veselova, Yulia S. Panina, Anastasiya V. Muravieva

Neurological Center of Epileptology, Neurogenetics and Brain Research, University Clinic of Voyno-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russia
Email: *mart2802@yandex.ru

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Abstract

Epilepsy is one of the most frequent neurological disorders. In these circumstances, more than 25% of the patients are women of reproductive age. The aim of our research was to analyze the effectiveness and safety of antiepileptic therapy in women with epilepsy during pregnancy and to analyze the pregnancies' outcomes. We included in our research 121 pregnancies of 101 women aged at the moment of childbearing about 26.9 ± 4.57 years old. Idiopathic forms of epilepsy were predominant among all causes—47.1% ($p < 0.01$). Of all cases, 65.4% remained seizure-free from generalized tonic-clonic seizures (GTCS), including 69.6% of all idiopathic epilepsy cases and 68.6% among symptomatic ones. The antiepileptic drugs (AED) dosages were exceeding teratogenic level at the moment of conception in 54.7% of the cases. Worse control of epileptic seizures was associated with Benzobarbital (66.7%) and Lamotrigine (50.0%). Women with epilepsy did not receive specialized neurological therapy before conception in most cases, which leaded to the usage of AED teratogenic doses and less effectiveness of AED during pregnancy. It is necessary to plan the pregnancy and prescribe rational treatment for epilepsy starting at the stage of planning and during gestation in order to obtain a better seizures control and to decrease congenital disorders risk in fetus.

Keywords

Epilepsy, Women, Pregnancy, Anticonvulsants, Rational Therapy, Outcomes

*Corresponding author.

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1. Introduction

Therapy for epilepsy during pregnancy is extremely important, as it is necessary to take into account both women needs and teratogenic potential of antiepileptic drugs (AEDs) against the embryo and growing fetus [1]. In particular, the influence risk of AED to the fetus must be balanced with uncontrolled epileptic seizures in mother. Epilepsy is rather dangerous disorder and epileptic seizures, and especially generalized tonic-clonic seizures (GTCSs), can seriously damage mother's health, including leading to maternal mortality [2]. Moreover, frequent GTCSs during pregnancy can be associated with cognitive deficiency in children in future [3] [4]. In common, all of the AEDs are associated with teratogenic risk, especially traditional ones [5] [6].

The risk of congenital disorders is dose-dependent and increasing in case of polytherapy, therefore it is necessary to find an effective dosage of that anticonvulsant which is most relevant to the type of seizures and form of epilepsy before conception [7].

Our study aimed to analyze the effectiveness and safety of antiepileptic therapy in women with epilepsy during pregnancy.

2. Materials and Methods

2.1. Study Design

Our study is an observational cohort study. We prospectively monitored pregnancies exposed to mono- or polytherapy with different doses of AEDs. This study was conducted in the Neurological Center of Epileptology, Neurogenetics and Brain Research of the Voyno-Yasenetsky Krasnoyarsk State Medical University's University Clinic, which is located in Krasnoyarsk city, Russia. It was performed as a part of complex research No 210-16 "Epidemiological, genetic and neurophysiological aspects of nervous system disorders (central, peripheral, autonomic) and preventive medicine" in 2008-2013 (state registration No 0120.0807480) [8].

2.2. Participants

We included women with epilepsy in our study, observation unit-patient with epilepsy, case history. All women underwent preliminary anamnestic and clinical selection using stratified randomization. All of the participants were of fertile age (18 - 49 years old), Krasnoyarsk region's residents, and had certain diagnosis of epilepsy. Neurological center of the University clinic provided medical assistance to 4230 patients during the study period, including 2525/4230 (59.7% ± 0.75%) women and 1705/4230 (40.3% ± 0.75%) men. Fertile age of women amounts to 39.8% ± 0.8% (1685/4230). Seizure control and AED treatment were recorded prospectively in 121 pregnancies of 101 women.

2.3. Procedures

We collected data via neurological, gynecological and somatic assessment, genealogical method, long-term video-electroencephalography (EEG) monitoring, and magnetic resonance imaging (MRI) 1.5T.

2.4. Analysis

The statistical analysis was performed using STATISTICA v.10.0 software [StatSoft, USA]. Descriptive statistics for qualitative factors was expressed in absolute values, percentage terms and its standard errors. Distribution type was identified with Shapiro-Wilk test. We used Student t-test and Fisher's test for characterization (quantity of normally distributed characteristics) data comparison in observation groups. We calculated 95 % confidence interval as borders for expected deviation. Data for ordered sample with nonparametric distribution are presented with medians and quartiles (Me [P_{25}; P_{75}]), and comparative statistics—with Mann-Whitney test.

2.5. Ethical Considerations

According to Declaration of Helsinki all of the participants signed informed consent. The study was approved by the local ethics committee of the Voyno-Yasenetsky Krasnoyarsk State Medical University.

3. Results and Discussion

Patients assessments in the University clinic were performed by neurologist-epileptologist: in 25/121 (20.7% ±

3.7%) cases—before conception and during pregnancy, in 34/121 (28.1% ± 4.1%)—starting from first trimester and further, in 23/121 (19.0% ± 3.7%)—in second trimester, in 19/121 (15.7% ± 3.0%)—in third trimester, in 13/121 (10.7% ± 2.8%)—admission was performed one year after the delivery, in 7/121 (5.8 ± 2.1%)—during next three years after delivery. Analysis of patients previous medical history showed that 54/121 (44.6% ± 4.5%) women did not subject to regular medical check-up, 43/121 (35.5% ± 4.4%)—visited neurologist at place of residence, 12/121 (9.9% ± 2.7%)—subjected to regular medical check-up with psychiatrist, in 12/121 (9.9% ± 2.7%) cases—not known, whether they projected or not (insufficient data).

Women age varied from 18 to 42 years old at the moment of observed pregnancies, mean age was 26.9 ± 4.57 years old. We noticed that amount of pregnancies was growing through 2011-2012 and revealed that it is connected with the usage of new-generation AEDs, decreasing of adverse effects, individualized approach to selection and dosing of AEDs (pharmacogenetics) and therapeutic drug monitoring (TDM) (**Figure 1**).

Unfortunately, compliance of women with epilepsy remains very low. Only 19/121 (15.7% ± 3.3%) pregnancies were planned with neurologist-epileptologist, and 58/121 (47.9% ± 4.5%) pregnancies were planned by women themselves. Preconception preventive taking of folic acid were conducted only in 36/121 (29.8% ± 4.15%) cases.

Idiopathic forms were predominant (57/121; 47.1% ± 4.53%) among epilepsy etiology, symptomatic ones amounted 31.4% ± 4.2% of the cases; cryptogenic epilepsy was diagnosed in 20.7% ± 3.7% of the cases. We did not confirm the diagnosis of epilepsy in solitary case despite the long-term administration of AEDs before first assessment in the University clinic ($p < 0.01$). High proportion of cryptogenic forms is associated with: GTCSs in personal history, no epileptiform activity in routine EEG at the moment of assessment, impossibility of video-EEG performance in Krasnoyarsk and Krasnoyarsk region polyclinics, lack of technical possibility to perform high field brain MRI with epilepsy program in some regions. Idiopathic forms of epilepsy had the following structure: juvenile myoclonic epilepsy—33/57 (57.7% ± 6.5%) cases, idiopathic epilepsy with isolated GTCS—12/57 (21.1% ± 5.4%) cases, juvenile absence epilepsy—5/57 (8.8% ± 3.7%) and idiopathic epilepsy with myoclonic absences—3/57 (5.3% ± 2.9%) cases. The background of symptomatic forms was as follows: mesial temporal sclerosis—in 13/38 (34.2% ± 7.7%) cases, brain congenital anomaly—9/38 (23.7% ± 6.9%), previous neuroinfection—8/38 (21.1% ± 6.6%), and brain tumor—3/38 (7.9% ± 4.4%). We diagnosed post-traumatic epilepsy in two cases (5.3% ± 3.6%), in two cases (5.3% ± 3.6%)—poststroke, in one case (2.6 ± 2.6%)—epilepsy against the background of congenital disorder with CNS defect.

Hereditary loading was detected in 21/121 (17.4 ± 3.4%) cases, including in 6/121 cases (5.0% ± 1.9%)—in

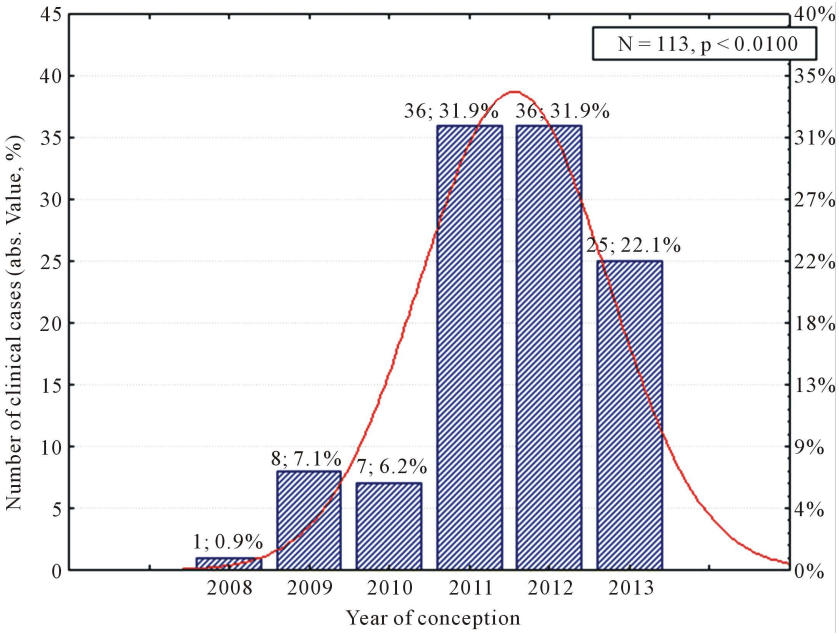

Figure 1. Pregnancies distribution in women of fertile age with epilepsy, 2008-2013 (according to proprietary data of the University clinic).

paternal line, in 5/121 (4.1% ± 1.8%) cases—maternally, 6/121 (5.0% ± 1.9%)—sibling's epilepsy, 4/121 (3.3% ± 1.6%)—in second bloodline, and in 6/121 (5.0% ± 1.9%) cases data were insufficient (poor hereditary history). There was no hereditary loading in 94/121 (77.7% ± 3.8%) of the cases, but genealogical analysis was performed only up to the fourth generation. Hereditary loading was observed more frequently in idiopathic forms (13/57; 24.7% ± 5.6%) than in symptomatic (3/38; 7.9% ± 4.4%) and cryptogenic ones (5/25; 20.0% ± 8.0%).

Generalized seizures (tonic-clonic, tonic, clonic, myoclonic) were predominant in seizures structure (51/121; 42.1%), simple focal seizures with (SGTCS) amounted to 15/121 cases (12.4%; $p < 0.01$) (**Figure 2**). Simple focal seizures with SGTCS were observed more frequently in symptomatic epilepsy (12/38; 31.6% ± 7.5%). Secondary generalized tonic-clonic seizures and complex focal seizures with SGTCS were dominant among cryptogenic forms: 7/25 (28.0% ± 8.9%) and 7/25 (28.0% ± 8.9%) respectively.

Women were seizure-free during the last year before conception in 64/121 (52.9% ± 4.5%) cases. Cryptogenic epilepsy was associated with the worst GTCS control (60.0% ± 4.5%) (**Table 1**). Of all cases, 77.7% (94/121) were seizure-free during the first trimester of pregnancy. We observed the best GTCSs control in symptomatic epilepsy (32/38; 84.2% ± 5.9%). Remission of GTCSs was observed rarely in second trimester (78/110; 70.9% ± 4.3%) than in first trimester due to self-acting AEDs withdrawal. The best GTCSs control was observed in idiopathic epilepsy during the second trimester (38/49; 77.6% ± 5.9%) and GTCSs remission was observed rarely in third trimester (68/104; 65.4% ± 4.7%) than in first and second ones, but frequently than during the last year before conception. Seizure control was worse during third trimester in cryptogenic epilepsy (11/23; 47.8% ± 10.4%) (**Table 1**). Frequency of GTCSs occurrence is presented in **Table 2**. We registered SGTCS in series in 0.9% of women during the second trimester, due to AEDs withdrawal. After readministration of AEDs, seizures were under control.

Remission of other epileptic seizures was reached in 73/121 (60.3% ± 4.4%) cases during the last year before conception (**Table 3**). High frequency of other seizures types (up to several times a day) was caused by absences and (rarely) by other seizures types in noncompensated epilepsy against the background of unplanned pregnancy. Higher frequency of other seizures types, weather before or during gestation, was observed in symptomatic epilepsy (**Table 4**).

Usage of Benzobarbital (2/3), Lamotrigine (5/10), Carbamazepine (4/12) and Phenobarbital (1/3) were associated with worse seizures control (including increasing of seizures frequency, seizures in series occurrence).

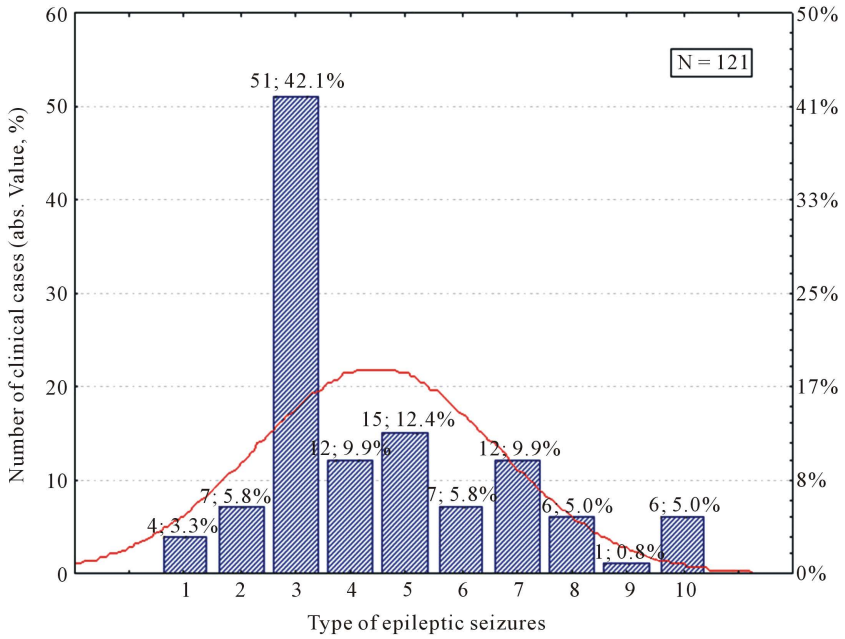

Figure 2. Types of epileptic seizures: 1—absences, 2—simple focal seizures, 3—GTCS, 4—SGTCS, 5—simple focal seizures + SGTCS, 6—simple focal and complex focal seizures SGTCS, 7—complex focal seizures + SGTCS, 8—simple focal and complex focal seizures, 9—complex focal seizures, 10—absences + GTCS.

Table 1. Remission of generalized tonic-clonic seizures during pregnancy.

Form of epilepsy	During the last year before conception			During gestation							
				In first trimester		In second trimester			In third trimester		
	Number of cases (n)	Abs.	%	Abs.	%	Number of cases (n)	Abs.	%	Number of cases (n)	Abs.	%
Idiopathic epilepsy	57	32	56.1 ± 6.6	45	78.9 ± 5.4	49	38	77.6 ± 5.9	46	32	69.6 ± 6.8
Symptomatic epilepsy	38	21	55.3 ± 8.0	32	84.2 ± 5.9	35	24	68.6 ± 7.8	34	24	70.6 ± 7.8
Cryptogenic epilepsy	25	10	40.0 ± 9.8	16	64.0 ± 9.6	25	15	60.0 ± 9.8	23	11	47.8 ± 10.4
Total (N)	121	64	52.9 ± 4.5	94	77.7 ± 3.8	110	78	70.9 ± 4.3	104	68	65.4 ± 4.7

Table 2. Frequency of generalized tonic-clonic seizures occurrence during gestation.

Frequency of GTCSs occurrence	In first trimester (N = 121)		In second trimester (N = 110)		In third trimester (N = 104)	
	Abs.	%	Abs.	%	Abs.	%
Absent	94	77.7 ± 3.8	78	70.9 ± 4.3	68	65.4 ± 4.7
Less than 1 per month	16	13.2 ± 3.1	16	14.5 ± 3.4	21	20.2 ± 3.9
Once per month	9	7.4 ± 2.4	6	5.5 ± 2.2	7	6.7 ± 2.5
Once per week	1	0.8	3	2.7 ± 1.5	4	3.8 ± 1.9
More than once per week	1	0.8	1	0.9	0	0
Daily GTCS	0	0	1	0.9	1	1.0
Rare	0	0	3	2.7 ± 1.5	0	0
Insufficient data	0	0	2	1.8 ± 1.3	3	2.9 ± 1.6

Table 3. Remission rate of other epileptic seizures during gestation.

Form of epilepsy	During the last year before conception			During gestation							
				In first trimester		In second trimester			In third trimester		
	Number of cases (n)	Abs.	%	Abs.	%	Number of cases (n)	Abs.	%	Number of cases (n)	Abs.	%
Idiopathic epilepsy	57	43	75.4 ± 5.7	46	80.7 ± 5.2	49	37	75.5 ± 6.1	46	37	80.4 ± 5.9
Symptomatic epilepsy	38	13	34.2 ± 7.7	18	47.4 ± 8.1	35	13	37.1 ± 8.2	34	10	29.4 ± 7.8
Cryptogenic epilepsy	25	16	64.0 ± 9.6	16	64.0 ± 9.6	25	16	64.0 ± 9.6	23	15	65.2 ± 9.9
Total (N)	121	73	60.3 ± 4.4	81	66.9 ± 2.3	110	66	60.6 ± 4.7	104	63	60.6 ± 4.8

Table 4. Occurrence rate of other types of seizures during gestation.

Occurrence rate	In first trimester (N = 121)		In second trimester (N = 110)		In third trimester (N = 104)	
	Abs.	%	Abs.	%	Abs.	%
Absent	81	66.9 ± 2.3	66	60.6 ± 4.7	63	60.6 ± 4.8
Less than 1 per month	15	12.4 ± 2.9	12	10.9 ± 2.9	15	14.4 ± 3.4
Once per month	9	7.4 ± 2.4	9	8.2 ± 2.6	8	7.7 ± 2.6
Once per week	5	4.1 ± 1.8	9	8.2 ± 2.6	7	6.7 ± 2.5
More than once per week	2	1.7 ± 1.2	5	4.5 ± 1.9	2	1.9 ± 1.3
Daily GTCS	7	5.8 ± 2.1	5	4.5 ± 1.9	5	4.8 ± 2.1
Rare	0	0	0	0	0	0
Insufficient data	2	1.7 ± 1.2	3	2.7 ± 1.5	4	3.9 ± 1.9

However, women used these drugs rarely. There was no epileptic status observed.

Pregnancy was terminated in first trimester in 8/121 (6.6% ± 2.3%) cases, due to missed abortion—in 2/121 (1.6% ± 1.2%) cases, due to ectopic pregnancy—in 2/121 (1.6% ± 1.2%) cases. Spontaneous abortion occurred in first trimester in 2/121 (1.6% ± 1.2%) cases, two women (2/121; 1.6% ± 1.2%) underwent therapeutic abortion (according to women' will), including: to one woman (1/121; 0.8%)—due to AED usage, the other one (1/121; 0.8%)—due to GTCSs. Three women (3/121; 2.5% ± 1.2%) were prolonging their pregnancy at the moment of data analysis (first trimester). Pregnancy was aborted in second trimester in 3/110 (2.7% ± 1.6%) cases including 2/110 (1.8% ± 1.8%)—due to revealed congenital disorder in fetus. In the first case (1/110; 0.9%) Arnold-Chiari II type malformation was diagnosed prenatally, in the second case (1/110; 0.9%)—Dandy-Walker syndrome. One (1/110; 0.9%) pregnancy was terminated in second trimester due to seizures relapse with serial SGTCS against the background of Benzonal to Valproic acid one-moment substitution. Three women (2.7% ± 1.6%) women were in second trimester at the moment of data analysis.

Usage/changing of antiepileptic therapy during gestation were as follow: patients did not use AEDs in 13/121 (10.7% ± 2.8%) cases, AED and/or its dosage did not change in 36/121 (29.8% ± 4.2%) cases, AEDs were administered for the first time in 22/121 (18.2% ± 3.5%) cases, self-acting withdrawal was performed due to conception in 13/121 (10.7% ± 2.8%), self-acting dosage decreasing was observed in 6/121 (5.0% ± 1.9%) cases, increasing of AEDs dosage—in 18/121 (14.9% ± 3.2%) cases, AEDs dosage decreasing according to neurologist's administration—in 6/121 (5.0% ± 1.9%) cases, administration of second AED was performed in 4/121 (3.3% ± 1.6%) cases, AEDs were canceled by gynecologist in 1/121 (0.8%) case, AED dosage was increased according to gynecologist's decision in 1/121 (0.8%) case, and synonymic substitution was performed by pharmacist without taking into account doctor's administration in 1/121 (0.8%) case. Antiepileptic drugs dosage was not changed in most cases of idiopathic epilepsy (22/57; 38.6% ± 6.4%). Therapy was administered during the gestation for the first time in 11/57 (19.3% ± 0.9%) cases. Anticonvulsants dosage was not changed in most cases of symptomatic epilepsy (10/38; 26.3% ± 7.1%), and we registered self-acting withdrawal in 10/38 (26.3% ± 7.1%) cases. It was necessary to increase the dosage of AEDs in 10/25 (40.0% ± 9.8%) cases of cryptogenic epilepsy, and AEDs were administered for the first time during gestation in 6/25 (24.0% ± 8.5%) cases.

Eighty-six (71.1% ± 4.2%) patients were receiving AEDs at the moment of conception including 70/86 (81.4% ± 4.2%)—as a monotherapy, and 16/86 (18.6% ± 4.2%)—as duo therapy. Fifty-five women were receiving Valproates as a basic medication (64.0% ± 5.2%) (**Table 5**), that was associated predomination of idiopathic generalized epilepsy (47.1%) and high frequency of generalized seizures (88.8%). Dosages of AEDs were higher than teratogenic level at the moment of conception in 54.7% ± 5.4% of the cases, mostly on Valproates (41.9% ± 5.3%) (**Table 5**). Daily dosages of Valproates that were higher than teratogenic level (≥700 mg daily) were registered in 36/55 (65.5% ± 6.4%) cases, including dosage higher than 1500 mg daily, that is associated with higher risk of congenital disorders in fetus, was registered in 9/55 (16.4% ± 4.9%) cases. That was associated

Table 5. AEDs therapy structure during pregnancy.

AED and its teratogenic daily dose (mg daily)	First trimester		Second trimester		Third trimester	
	Abs.	%	Abs.	%	Abs.	%
Monotherapy	70	81.4	64	86.5	67	85.9
Valproates < 700	19/55	34.5	15	30.6	14[2]	28.0
Valproates ≥ 700 and <1500	27/55	49.1	29	59.2	31[2]	62.0
Valproates ≥ 1500	9/55	16.4	5	10.2	5[2]	10.0
Valproates (total)	55	64.0	49	66.2	50	64.1
Carbamazepine < 400	1/8	12.5	3[1]	33.3	3[2]	27.3
Carbamazepine ≥ 400 and <1000	7/8	87.5	6	66.7	7[2]	63.6
Carbamazepine ≥ 1000					1	9.1
Carbamazepine (total)	8	9.3	9	12.2	11[2]	14.1
Lamotrigine < 300	5/9	55.6	3[1]	50.0	4	57.1
Lamotrigine ≥ 300	4/9	44.4	3[1]	50.0	3	42.9
Lamotrigine (total)	9	10.5	6[1]	8.1	7	9.0
Phenobarbital < 150	3	3.5	2	2.7	2	2.6
Benzobarbital < 150	3	3.5	2	2.7	2	2.6
Levetiracetam*	3	3.5	3	4.1	3	3.8
Topiramate*	5	5.8	3[1]	4.1	3[2]	3.8
Duo therapy	16	18.6	10[1]	13.5	11	14.1
Total	86		74		78	

*Dose-dependent teratogenic effect are not described due to few clinical trials; [1]$p < 0.05$ between first and second trimester; [2]$p < 0.05$ between first and third trimester.

with unplanned pregnancy and absence of preconceptional preparing. Daily doses of Carbamazepine, that were higher than teratogenic level (≥400 mg daily) were received by 7/8 (87.5% ± 11.7%) women. Daily doses of Lamotrigine, that were higher than teratogenic level (≥300 mg daily)—4/9 (44.4% ± 16.6%) women, and daily doses of Phenobarbital, that were higher than teratogenic level (≥150 mg daily) were not administered. The following combinations were used at the moment of conception: in 4/16 cases—Valproates + Lamotrigine, in 4/16 cases—Valproates + Carbamazepine, in 4/16 cases—Valproates + Topiramate, in 1/16 case—Valproates + Levetiracetam, in 1/16 case—Carbamazepine + Topiramate, in 1/16 case—Lamotrigine + Valproates, in 1/16 case—Phenobarbital + Benzonal. During the second trimester patients were receiving AEDs in 74/121 (70.2% ± 4.4%) cases. Decreasing of AEDs was associated with pregnancy termination in first trimester or due to self-acting withdrawal. Also we observed 2/74 (2.7% ± 1.9%) cases of AEDs changing: in one case—one-moment Benzonal (100 mg daily) to Valproate (500 mg daily) substitution with seizures relapse, followed by serial SGTCSs and termination of pregnancy, in other case—due to self-acting AED withdrawal and occurring of serial SGTCSs, so Topiramate was readministered (50 mg daily) and remission was regained. Patients were receiving AEDs in third trimester in 78/121 (64.5% ± 4.4%) cases: in 67/78 (85.9% ± 3.9%)—as a monotherapy, in 11/78 (14.1% ± 3.9%)—as duo therapy.

Increasing of AEDs more frequently was performed on Levetiracetam (25.0%) and Lamotrigine (20.0%). Requirement of second AED occurred on Lamotrigine in 30.0% of the cases.

Epilepsy complications during gestation were as follows: AEDs-dependent adverse effects—in 1/121 (0.8%)

case, seizures relapse—in 36/121 (29.8% ± 4.2%) cases, seizures in series—in 5/121 (4.1% ± 1.8%) cases, threatening miscarriage in early pregnancy—3/121 (2.5% ± 1.4%), threatening miscarriage in late pregnancy—8/121 (6.6% ± 2.3%), and congenital malformation in fetus—4/121 (3.3% ± 1.6%). Women did not have any complications in 58/121 (47.9% ± 4.5%) cases.

Congenital malformations were observed in 4/121 (3.3% ± 1.6%) cases: 1/121 (0.8%) case—Dandy-Walker syndrome (pregnancy was terminated in second trimester), 1/121 (0.8%)—Arnold-Chiari anomaly type II (pregnancy was terminated in second trimester), 2/121 (1.6% ± 1.2%) cases—congenital heart disorder, including: Fallot's tetrad (child died in neonatal age), ventricular septal defect, open foramen ovale, open arterial duct. In addition, Down's syndrome was diagnosed postnatal in 1/121 (0.8%) case, although there were no any markers of chromosomal disorder during prenatal diagnostics (ultrasonography in first, second and third trimesters, biochemical screening) and patient was not receiving AED at the moment of conception. Congenital disorders occurrence rate on Barbiturates was 16.7%, on Valproates—5.4%. Congenital disorders were registered in children when mothers were receiving Valproates during pregnancy in dose higher than 1000 mg (two cases) and 1250 mg daily (one case) or Phenobarbital 100 mg daily. Odds ratio of congenital disorders occurrence on Valproates appeared to be 1.7 times higher in comparison with all AEDs. On Phenobarbital—10.3 times higher. Hence congenital disorders on Phenobarbital occur 8.6 times more likely than on Valproates, which probably can be explained with small sampling of women receiving Phenobarbital—6 clinical cases.

Adverse effects were observed in two (1.6% ± 1.2%) women: polyneuropathy on Topiramate, dermopathy on Lamotrigine along with Vaplroates and due to increasing of both drugs without preliminary therapeutic drug monitoring.

As follow from the analysis of pregnancies outcomes we determined that delivery time varied from 28 to 41 weeks, median 39 (38; 40) weeks. In 34/76 (44.7% ± 5.7%) cases delivery was natural, in 37/76 (48.7% ± 5.7%)—performed via Cesarean section, including due to mother's pre-existing diseases (arterial-venous malformation, brain tumor, etc.). Delivery method is unknown in 5/76 (6.6% ± 2.8%) cases (patients did not come to second appointment after the delivery). Cesarean sections were performed more frequently in symptomatic epilepsy (75.0% ± 8.8%). Maternal and child mortality were not registered in our cases. In 1/121 (0.8%) case we registered chromosomal mutation, in 1/121 (0.8%)—anembryonic gestation, in 2/121 (1.6% ± 1.2%)—missed abortion, and in 2/121 (1.6% ± 1.2%) cases—spontaneous abortion in first trimester.

Summing up, we should notice that in most cases patients did not receive specialized therapy before conception. AEDs dosage exceeded teratogenic level in 54.7% of the cases. Evaluation of AEDs teratogenic potential, accounting of AEDs pharmacogenetic profile and congenital disorders of folate's cycle were performed very rare. Congenital disorders prevention with folic acid was performed only in 29.8% of the cases. Of all cases, 65.4% were seizure-free during gestation. In most cases delivery time was normal—at 39 weeks. However, in 48.7% of cases delivery was performed via Cesarean section.

4. Conclusions

Patients did not receive specialized therapy before conception in most cases (79.3%). Pregnancy was planned with neurologist-epileptologist only in 15.7% of the cases, self-planned—in 47.9% of the cases, which is correlated with international and Russian data [9] [10]. Congenital disorders prevention with folic acid was performed only in 29.8% of the cases.

About 60.6% of the patients were seizure-free during pregnancy, which is slightly less than European registry data (EURAP) (66%) [1] and resulting from self-acting withdrawal or decreasing of AED dosage. We observed remission from GTCSs in 65.4% of the cases. Women with idiopathic generalized epilepsy were seizure-free during pregnancy in 77.7% of the cases, which correlates with other Russian authors' data [11]. Requirement of AED dosage increasing and/or need for administration of second AED appeared only on Lamotrigine (50.0%), which correlates with European registry data (EURAP) [1].

AED dosage exceeded teratogenic level in 54.7% of the cases, which in common correlates with European registry data (EURAP) [1]. However, teratogenic dosages were observed in our patients on Valproates in 41.9% of the cases, which have the highest risk of congenital disorders to cause in comparison with 14.5% according to European registry data (EURAP) [1].

Congenital disorders occurrence rate in women receiving AED according to our study was 3.3% and congenital disorders caused by Valproates were 5.4% that correlates with European registry data (EURAP) [1] and is

lower than North-American registry data [12]. Congenital disorders were registered on Valproates in dose higher than 1000 mg daily, that correlates with other authors data about risk increasing on doses higher than 700 mg daily [5] [13]. Congenital disorders risk was increasing in case of hereditary loading, which also correlates with European registry data (EURAP) [5].

Congenital disorders occurrence rate on Barbiturates was 16.7% which is slightly higher than both European and North-American registries data (5.4% - 13.7% and 5.5% respectively) [5] [12], which probably can be explained with small sampling—6 clinical cases.

In common, congenital disorders occurrence rate on AEDs that we registered (3.3%) was consistent with Krasnoyarsk regional data (3.5% in 2012).

Women with epilepsy did not receive specialized neurological therapy before conception in most cases, which leaded to usage of AED teratogenic doses and less effectiveness of AED during pregnancy.

Summing up what has been said, it is necessary to plan the pregnancy and prescribe rational treatment for epilepsy starting from the stage of planning and during gestation in order to obtain a better seizures control and to decrease congenital disorders risk in fetus.

Conflict of Interest

None of the authors has any conflicts of interest to disclose.

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