Effects of antiepileptic therapy in women during pregnancy: a retrospective case-controlled study

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NEW SZÉCHENYI PLAN

I.INTRODUCTION

Antiepileptic therapy (AEDs) during pregnancy have been considered the cause of potential side effects in the fetus since the 1970s. Indeed, AEDs as a class have been shown to cause major congenital malformations (MCMs) [1-3], and also adverse effects on cognitive development after prenatal exposure [4]. Although some studies have hypothesized that mothers' epilepsy itself plays an important role in causing fetal abnormalities [5-7], recent findings have suggested that AEDs therapy is the main cause of malformations [8-10] and a large number of studies have shown the rate of MCMs and long-term effects associated with in utero AEDs exposure. In particular, the number of drugs associated and the therapy management during gestation may influence pregnancy outcome [11]. Most studies in the literature have evaluated the incidence of MCMs in the offspring of epileptic women exposed or not exposed to AEDs during pregnancy. It has become apparent from these studies that the rate of congenital malformations significantly increases in newborns exposed to AEDs during the first trimester of pregnancy and it is higher if more than one AED is taken [3], it is dose dependent and affected by other variables such as parental history of MCMs [12]. The highest risk has been observed with high dose of valproic acid exposure as compared to other AEDs such as carbamazepine, phenytoin and lamotrigine [12].

II.OBJECTIVE

In order to determine the role of antiepileptic drugs (AEDs) and the incidence of maternal, obstetrical, neonatal complications we conducted a retrospective case-controlled study on two cohort of pregnant women: 1) 86 epileptic women treated with AEDs, 2) 86 non-epileptic women treated without AEDs.

III. PATIENTS AND METHODS

All pregnants WWE (n=86) were followed-up during theirs pregnancy at the Department of Obstetrics and Gynaecology, Szeged, Hungary, and previously were also diagnosed and treated by the Department of Neurology, Szeged, Hungary, between 2000 and 2012 were enrolled in our study. Demographic characteristics, obstetrical- and epilepsy related data were evaluated in the pregnant WWE group. For comparison of the different perinatal parameters, the χ^2 test and the independent sample t-test were performed. Results were considered statistically significant with $p < 0.05$. Relationships between congenital anomalies and the different AED regimens were examined by non-parametric Kruskal-Wallis analysis. All statistical analyses were performed with SPSS (Statistcial Package for Social Sciences) version 20.

IV.RESULTS

Table 1. Seizure relapses during pregnancy and the puerperium

	n	%
No changes in seizure pattern	60	69.8
During the 3 rd trimester	23	26.7
During delivery	1	1.2
In the puerperium	2	2.3

Table2.

Table 2. Comparison of delivery mode and neonatal parameters in the case and control groups

	Women with epilepsy (n=86)		Women without epilepsy (n=86)		p
	n	%	n	%	
Prematurity (<37 weeks, <2500 g)	12	13.95	9	10.46	N.S.
Intrauterine growth retardation	5	5.81	1	1.16	N.S.
Assisted vaginal delivery	39	45.34	50	58.14	0.026
Caesarean section	40	46.51	33	38.37	N.S.
Miscarriage	6	7	0	0	0.015
Post-term birth	21	24.41	21	24.41	N.S.
Mean gestational age (weeks)	38.5 ± 2.1		38.4 ± 2.2		N.S.

Table 3. Relationship of epilepsy syndromes and AED use during pregnancy and congenital malformations

*Type of epilepsy	AED exposure during pregnancy	No. of AED-treated WWE (n=86)	Percentage of all WWE	No. of CMs
SF	Not exposed to AED	15	17.44	0
PG	Valproic acid	14	16.23	4
SF	Lamotrigine	6	6.98	0
PG	Carbamazepine	10	11.63	1
PG	Valproic acid + Lamotrigine	16	18.604	1
PG	Valproic acid + Carbamazepine	11	12.79	1
PG	Lamotrigine + Carbamazepine	8	9.30	0
SF,SG	Lamotrigine + Levetiracetam	6	6.98	0

Table 4. Relationship between valproic acid exposure and detected congenital malformations

	VPA+*	VPA-**	Not exposed to AED	p
Congenital malformations	6	1	0	0.054
Healthy neonates	35	29	15	

Abbreviation:
* PG: primary generalized epilepsy, PF: primary focal epilepsy, SG: secondary generalized epilepsy, SF: secondary focal epilepsy; WWE: women with epilepsy; AED: antiepileptic drug, CM: congenital malformations*VPA+: valproic acid-containing therapy, ** VPA-: not valproic acid therapy instead lamotrigine, carbamazepine or levetiracetam

IV.CONCLUSIONS

- In the trial by Thomas et al. [13] on 1297 women, their patients demonstrated three peaks of seizure relapse in the course of the pregnancy (during first and second and six months), and the frequency of seizures was highest during the three days peripartum. Their findings on that large population are supported by our results relating to 86 WWE.
- In agreement with Morrell et al. [14], detected a significant difference in the rate of miscarriages between the WWE and the controls ($p = 0.015$).
- In their report relating to 220 women Katz et al. [15] showed that epilepsy is an independent risk factor for delivery by Caesarean section. Whereas, Hiilesma et al. [16] did not observe a significant difference in the Caesarean section rate among 150 WWE. Our results too demonstrated that the rate of Caesarean section did not different significantly between the two groups.
- In agreement with previous report [12], the rate of congenital malformations among the newborns of all AEDs exposed mothers was 8.14 %. This rate was higher for pregnancies exposed to valproic acid as compared with carbamazepine, lamotrigine and levetiracetam-containing AEDs ($p = 0.054$).

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