

Sabine Pittschieler
Christoph Brezinka
Beate Jahn
Eugen Trinkka
Iris Unterberger
Judith Dobesberger
Gerald Walser
Andrea Auckenthaler
Norbert Embacher
Gerhard Bauer
Gerhard Luef

Spontaneous abortion and the prophylactic effect of folic acid supplementation in epileptic women undergoing antiepileptic therapy

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S. Pittschieler · E. Trinkka · I. Unterberger ·
J. Dobesberger · G. Walser · A. Auckenthaler
· N. Embacher · G. Bauer · G. Luef, MD (✉)
Dept. of Neurology
Medical University Innsbruck
Anichstrasse 35
6020 Innsbruck, Austria
Tel.: +43-512/504-23877
Fax: +43-512/504-24260
E-Mail: gerhard.luef@i-med.ac.at

C. Brezinka
Dept. of Gynecology
Medical University Innsbruck
Innsbruck, Austria

C. Brezinka
Dept. of Obstetrics and Gynaecology
ErasmusMC
Rotterdam, The Netherlands

B. Jahn
Dept. of Medical Statistics
Informatics and Health Economics
Medical University Innsbruck
Innsbruck, Austria

■ **Abstract** *Background* Antiepileptic drugs (AEDs) like phenytoin (PHE), carbamazepine (CBZ), barbiturates and valproic acid (VPA) interfere with folic acid absorption and metabolism, which in turn can be the cause of adverse pregnancy outcome. *Objective* To study the prophylactic effect of folic acid supplementation with regard to spontaneous abortion and preterm delivery (fetal demise after week 20 of gestational age) in pregnant women receiving AED therapy, as well as benefits of most common dosage and preconceptional commencement. *Methods* Prospective examination of 104 patients, registered in EURAP from 1999–2004 at a single center and a retrospective analysis of data from our epilepsy databank completed with medical records and patients interviews of the Department of Neurology of Innsbruck University Hospital

from 1971 to 1999. *Results* 388 pregnancies in 244 patients were analyzed. Pregnancies with folic acid supplementation showed significant reduction of spontaneous abortion. With regard to monotherapies, in the group of women taking VPA, supplementation of folic acid had significant benefit. Other examined monotherapies (CBZ, PHE, and PB) known to interfere with folic acid showed no significant results. *Conclusions* This study confirms the prophylactic effect of folic acid supplementation on spontaneous abortion. For AED therapy, folic acid supplementation should be part of the therapy of every pregnant epileptic woman, especially for those treated with VPA.

■ **Key words** epilepsy · antiepileptic drugs · folic acid · abortion

Introduction

Low serum concentrations of maternal folate are associated with an increased risk for adverse birth outcomes. The rate of spontaneous abortion in a population-based study increases from 10% for folate blood levels above 6.1 ng/mL (14.0 nmol/L) to 17% for low blood levels (<2.19 ng/mL or <4.9 nmol/L) [9]. Studies of healthy women [12, 27] and animal studies [3, 19] report low maternal folate levels to entail greater risk for adverse development.

A significant proportion of healthy women of reproductive age have low dietary folate intake with consequent low folate blood levels [9]. Women taking AEDs are at even greater risk for low folate levels. Treatment with cytochrome P450 enzyme-inducing antiepileptic drugs is known to interfere with folate metabolism [16]. Drugs like phenytoin (PHE), carbamazepine (CBZ) and barbiturates also cause folate malabsorption [21], and valproic acid (VPA) interferes with the production of the active metabolite of folate by inhibiting glutamate formyl transferase [30].

This is a single center study analyzing the relation-

ship between spontaneous abortion, preterm delivery and folate supplementation in women treated with different AEDs. In addition, the effects of different dosages and benefit of preconceptional commencement of folic acid supplementation were compared.

Patients and methods

The study included all pregnancies of epileptic women treated at the Departments of Neurology and Gynecology of Innsbruck Medical University between 1971 and 2004. The medical university hospital is a primary care center for epilepsy patients and serves a total population of approximately 680,000. Women were seen regularly by a neurologist and information on their pregnancy was recorded. Patients treated between 1999 and 2004 were registered in the European Registry for Antiepileptic Drugs and Pregnancy (EURAP) as part of its prospective study.

Since 1971 all patients were prospectively entered into an epilepsy databank and data retrospectively completed from medical records of the epilepsy unit of the Department of Neurology. These data included maternal age, duration and type of epilepsy, seizures type and frequency before and during pregnancy, drug regimen, serum AED levels during pregnancy, folic acid intake, smoking and alcohol consumption. Patient interviews provided further information on obstetric history, complications during pregnancy, spontaneous abortion (fetal demise within the first 20 weeks of gestational age) and preterm delivery (birth before the completion of 37 weeks of gestation), delivery, measurements of the newborn, minor and major congenital abnormalities. Only pregnancies with complete information were included.

Incomplete information on miscarriages was supplemented from the forensic files of the Department of Pathology of Innsbruck Medical University Hospital.

Pregnancies with commencement of folic acid supplementation after week 12 of pregnancy were excluded, because the first 12 weeks are the most crucial for developmental disturbance leading to spontaneous abortion. Induced abortions were also excluded. Initially 434 pregnancies were enrolled. Forty-six women (11%) did not use anti-epileptic drug therapy during the first trimester. A total of 388 pregnancies received AEDs in mono- or polytherapy and were enrolled for study examination.

Analysis focused on the effect of folic acid supplementation. End points of the study were spontaneous abortion or live birth. Three groups were formed: a group with dosage of 0.4 mg/d, a group with dosage of 5 mg/d and one with no folate supplementation ($n=228$, 59%). Risk and odds ratios were calculated for patients lacking folic acid supplementation.

Statistical analysis

The study is a case control study. Pregnancy outcome was tested with the chi-square test (p values quoted) and odds ratios with associated 95% CI and numbers needed to treat where calculated. Logistic regression analysis was performed to control for possible confounder. Patient characteristics were summarized with frequencies, percentages and mean values. There was no need for alpha correction (Bonferroni correction, multiple testing) because there was no composite null hypothesis. We tested different questions which did not refer to a superior hypothesis. All p-values are two-sided and a type I error level of 5% was used. Statistical calculations were performed using SPSS, version 10.5, for Windows.

Results

A total of 388 pregnancies in 244 women with epilepsy met all criteria for analysis. Tonic clonic seizures in the first trimester affected 8% of women; 79% of these were single events (see Table 1 for more details to type of epilepsy and seizures). In most patients AED monotherapy was preferred (299 pregnancies, 77%; Fig. 1).

One hundred and sixty pregnancies (41%) in 105 women had folic acid supplementation. Only in 65 of these pregnancies (41%) was preconceptional commencement recorded. The use of folic acid increased from 3% in the years between 1971 and 1979 to 15% from 1980 to 1989, to 34% in the following decade and to 94% in the years from 1999 to 2004. The preconceptional commencement increased from 6% in the 1980s to 16% in the 1990s and 59% in the last five years. Most

Table 1 Characteristics of study patients and pregnancies

Category	Numbers	Overall %	Relative %
Number of pregnancies	388		
Number of patients	244		
Mean age	27		
Type of epilepsy			
Fokal	131	54 %	
Symptomatic	51/131		39 %
Kryptogenetic	58/131		44 %
Idiopathic	22/131		17 %
Idiopathic generalized	113	46 %	
Seizure during pregnancy			
Fokal	23/244	9 %	
First trimester	16/244	7 %	
Single event	9/16		56 %
Generalized (Fokal or generalized onset)	35/244	14 %	
First trimester	20/244	8 %	
Single event	16		79 %
Smoking	28/244	11	
Alcohol consumption increased	2/244	0.5 %	
Drug abuse	3/244	0.8 %	
AED polytherapy	86/388	23 %	
2 AEDs	58/86		67 %
3 AEDs	24/86		28 %
4 AEDs	4/86		5 %
Monotherapy	299/388	77 %	
CBZ	128/299		43 %
VPA	108/299		36 %
PHE	25/299		8 %
LTG	13/299		4 %
PB	11/299		4 %
OXC	8/299		2 %
Others	9/299		3 %

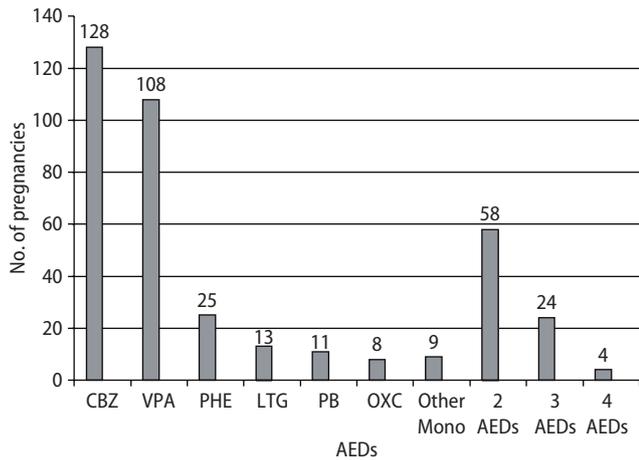


Fig. 1 The distribution of AED therapies among pregnancies of our study patients. The abscissa shows the different AEDs in monotherapy or combination, while ordinate shows the numbers of pregnancies (VPA valproate monotherapy; CBZ carbamazepine monotherapy; PHE phenytoin monotherapy; PB phenobarbital monotherapy; LTG lamotrigine monotherapy; OXC oxcarbazepine monotherapy)

patients (n=126, 79%) received the higher dosage (5 mg/d) and only 33 patients (8%) received the lower dosage (0.4 mg/d). For more details on supplementation over the course of time, see Table 2.

Twenty-eight pregnant women (7%) smoked during pregnancy, two (0.5%) had elevated alcohol consumption and three (0.8%) abused drugs.

Spontaneous abortion occurred in 39 out of 388 preg-

nancies (10%), preterm delivery in 1% (4/388). The occurrence of a spontaneous abortion was much lower in women taking folic acid during pregnancy. Of women with folic acid supplementation, 9 out of 160 pregnancies (5.7%) experienced spontaneous abortion and 1 (0.6%) preterm delivery. In women without supplementation 30 (13.2%) spontaneous abortions and 3 (1.3%) preterm deliveries out of 228 pregnancies occurred. Odds ratio for spontaneous abortion was 2.6 (95% CI: 1.2–5.6, p=0.01) for women with no supplementation (Table 3) and the number needed to treat was 13.3 (95% CI: 7.6–53.3). Preterm delivery occurred in 3 out of 4 times without folic acid supplementation. Due to the small total number, results are not significant for preterm delivery (OR: 2.3 (95% CI: 0.2–22.4, p=0.5).

With regard to the dosage of folic acid supplement, the group of pregnancies with low dosage (n=33) showed no spontaneous abortion. All spontaneous abortions and preterm deliveries with concomitant folic acid supplementation (n=9 and 1, respectively) occurred in the group with high dosage (n=127).

Six spontaneous abortions occurred in pregnancies with preconceptional commencement (n=65), 2 in pregnancies with postconceptional commencement (during the first trimester) (n=68).

Logistic regression analysis showed no significant impact of age of women, type of epilepsy, etiology and type of seizures, as well as number and type of seizures during pregnancy.

Of patients smoking during pregnancy (n=28), only

Table 2 Folic acid supplementation within different decades. Numbers are expressed as percentage of all pregnancies of this decade as well as numbers of pregnancies. The first line shows the frequency of folic acid supplementation without differentiation dosage and time of commencement. The second line shows numbers of supplementation of the two groups (0.3–0.5 mg and 5.0–5.4 mg) of folate dosage. In the last line numbers of preconceptional and postconceptional commencement are shown for the different decades

	1971–1979 (n=72)	1980–1989 (n=115)	1990–1999 (n=95)	1999–2004 (n=106)
Folic acid supplementation				
yes	3% (n=2)	15% (n=17)	34% (n=32)	94% (n=100)
Dosage of folic acid supplementation				
0.3–0.5	100% (n=2)	53% (n=9)	34% (n=11)	21% (n=8)
5.0–5.4	0% (n=0)	47% (n=8)	66% (n=21)	79% (n=92)
Commencement				
Before conception	0% (n=0)	6% (n=1)	16% (n=5)	59% (n=59)
After conception	100% (n=2)	94% (n=16)	84% (n=27)	41% (n=41)

Table 3 Numbers and percentage of spontaneous abortions, as well as preterm delivery. Odds ratio, 95% CI and significance are calculated for the event of spontaneous abortion without folic acid supplementation

	Folic acid supplementation		Dosage [mg/d]		Start of supplementation	
	Yes (160)	No (228)	0.4 (33)	5–5.4 (127)	Prior to conception (65)	After conception (68)
Spontaneous abortion/delivery n	9/150 (5.7%)	30/195 (14.5%)	0/33 (0%)	9/117 (7.1%)	7/85 (7.6%)	3/91 (3.2%)
Preterm delivery/delivery	1/150 (0.6%)	3/195 (1.3%)	0/33 (0%)	1/117 (0.8%)	0/85 (0%)	1/91 (1%)
Odds ratio	OR	2.6				
	95% CI	1.2–5.6				
	p	0.01				

one (20 cigarettes/day) experienced spontaneous abortion. This patient, however, was not supplemented with folic acid during pregnancy. Of the three patients with drug abuse one patient had an abortion. In this case the patient also smoked (10 cigarettes/day) and was supplemented with 5 mg of folic acid per day. There were no spontaneous abortions among patients with elevated alcohol consumption ($n = 2$).

Without folic acid supplementation spontaneous abortion occurred in 16% of cases under monotherapy. Folic acid supplementation reduced the event of a spontaneous abortion significantly to an occurrence of 6% (OR: 2.9, 95% CI: 1.3–6.8, $p = 0.004$). In the small number of women under polytherapy, frequency of spontaneous abortion was 3.7% without and 3.3% with folic acid supplementation (OR: 1.6, 95% CI: 0.2–16.5, $p = 0.79$). The most commonly used drugs in monotherapy were VPA ($n = 108$) and CBZ ($n = 128$) (Fig. 1). Folate supplementation was observed to significantly lower risk in the VPA group. Without folate the odds ratio for spontaneous abortion was 16.3 (95% CI: 2.1–128.3, $p = 0.00$). We were not able to confirm that the prophylactic effect is greater for a higher dosage of VPA (dose > 1000 mg/day; OR: 1.1, 95% CI: 0.7–19.8, $p = 0.79$). In the CBZ group the prophylactic effect was not significant (OR: 1.7, 95% CI: 0.6–5.0, $p = 0.22$, Table 3). The numbers in the monotherapies other than CBZ and VPA were too small to allow a meaningful analysis (Fig. 1).

Discussion

Spontaneous abortion (defined as pregnancy loss prior to 20 weeks of gestation) is a very common event and may complicate up to 20% of all pregnancies [17]. The data regarding the risk of abortion in women with epilepsy are extremely limited and conflicting. Some studies [1, 14] reported that increases in spontaneous abortion were associated with AED use in the first trimester, a result consistent with the possible teratogenic effects of AEDs. Risk of spontaneous abortion was increased in some women with idiopathic/cryptogenic epilepsy, depending on the clinical characteristics of their epilepsy [32].

Folic acid deficiency has been postulated as a possible cofactor in the teratogenic effects associated with the maternal use of AEDs during pregnancy [13, 18, 31, 33].

There are two diverse mechanisms by which AEDs can cause low plasma levels of folic acid: reduction of folate intestinal absorption (PHE, CBZ, PB, PRM) [11, 13, 24] or action as an antimetabolite (VPA) [30, 36]. Too little folic acid can interfere with biosynthesis of purines and pyrimidines and reduce the metabolism of amino acids like homocysteine, methionine, histidine, glycine, serine and has been associated with complications during pregnancy like repeated spontaneous abortion, in-

trauterine growth retardation, neural tube defect, heart defect, cleft lip and palate [4, 8, 21, 26, 33].

Results of the present study confirm that women with AEDs in pregnancy benefit from folate supplementation. Our data show an occurrence of spontaneous abortion in 13.2% of women under AED therapy not supplemented with folic acid. Folate supplementation was able to lower this to 5.7%. When comparing risks of patients with and without folic acid supplementation the odds ratio for women without folic acid supplementation was 2.3 (95% CI: 0.2–22.4, $p = 0.5$). Our data are derived from information collected over a third of a century. This long period can bear a risk of time-related confounding factors. Factors like maternal age, smoking behavior, as well as number and type of seizures during pregnancy, however, did not influence our analysis.

Our data demonstrate also how supplementation changed in the last 3 decades. Especially in the last 15 years supplementation rapidly augmented. With participation in EURAP, folate supplementation has become standard treatment for our patients.

In contrast to our findings, others have suggested that folic acid supplementation during pregnancy may have no benefit [10] or even be associated with an increased risk for miscarriage [22, 35, 37]. Trials report an increase of miscarriage up to 15% for doses of about 4 mg/d [35] and 16% for doses of about 0.8 mg/d of folic acid supplement or as fortified food [37]. One hypothesis to explain these observations is that folic acid extends survival of fetuses that might otherwise have been lost too early to be recognized [15]. The optimal dosage of folate supplements is still the subject of controversy. For healthy women, studies recommend 0.4 mg/day [4], 0.25–0.5 mg/day [2] or even lower dosages like 0.1–0.3 mg/day [7, 19]. Women with a previous pregnancy affected by a neural tube defect or with multiple spontaneous abortions are advised to take 4 to 5 mg/day supplemental folic acid when planning a subsequent pregnancy [25].

Among patients of our study, low dosage implied 0.4 mg/d as part of multivitamin supplements, high dosage special folic acid supplements with 5 mg. Folate-fortified food is not yet available on the Austrian market.

Of the 33 women (21%) who received less than 5 mg/day (0.4 mg/day in multivitamin preparations) no miscarriage was reported. For the 79% of pregnancies ($n = 127$) receiving 5 mg/day, 7.1% ($n = 9$) of patients with folic acid supplementation experienced spontaneous abortion. These numbers seem to show higher benefit for low dosage supplementation. However, the small number of patients ($n = 33$) with low dosages compared to high dosages ($n = 127$) should be borne in mind when interpreting this result. The prophylactic effect of folic acid supplementation in healthy women is most effective within the first 56 days after conception when vital fetal organs are formed [3]. To guarantee protection during the early embryonic period it is widely recom-

mended that supplementation be commenced before conception [5, 29]. Our results showed no advantage for preconceptional (7.6 %, n = 7/85) over postconceptional commencement within the embryonic period (3.2 %, n = 3/91). There might be an estimated number of unknown spontaneous abortions in women taking folic acid, as abortions may have passed unrecognized or before antenatal booking. Most of the reported abortions (51.4 %) were between week 10 and 12 of gestation. In women with preconceptional commencement, all abortions were reported before week 13 of gestation, and in those with postconceptional commencement, 75 % of abortions after week 12 of gestation. Most of them (40 %) received folate supplementation between week 3–6 of gestation and only 20 % between week 12–14 of gestation.

It has been reported that the higher drug levels are and the more AEDs are used, the lower folic acid blood and red cell levels are [6]. Consequently folic acid supplementation should show greater prophylactic effect for polytherapies. However, our study showed a higher rate of spontaneous abortion as well as a higher prophylactic effect under monotherapy (6 % of spontaneous abortions with folic acid supplementation vs. 16 % without supplementation, OR: 2.9, 95 % CI: 1.3–6.8, $p = 0.004$) than under polytherapy (3.3 % of spontaneous abortions with folic acid supplementation vs. 3.7 % without supplementation, OR: 1.6, 95 % CI: 0.2–16.5, $p = 0.79$). This could be because we treated relatively few women with polytherapy compared to monotherapies (Fig. 1). Some authors suggest [34] that higher dosage, namely for VPA above 1000 mg/d or 1400 mg/d, can entail a greater risk for spontaneous abortion and fetal malformations. The group with higher VPA dosages during pregnancy was too low to compare (Table 4).

The two AEDs most commonly administrated in monotherapy were VPA (n = 108) and CBZ (n = 128). Folate supplementation showed a significant benefit in the VPA group (OR: 14.5; 95 % CI: 1.8–115.8, $p = 0.001$). There were 15/44 (25 %) spontaneous abortions in the group without and only 1/43 (2 %) in the group with folic acid supplementation and VPA monotherapy. This result demonstrates the importance of considering the anti-metabolic effect of VPA on folic acid [27, 30]. Our results, however, did not show a greater prophylactic effect when using a higher dosage of VPA (dose > 1000 mg/day; OR: 1.15, 95 % CI: 0.68–19.80, $p = 0.79$). CBZ showed no significant prophylactic effect of folic acid (OR: 1.7, 95 % CI: 0.6–5.0, $p = 0.22$).

To summarize our findings, folic acid supplementation has a significant prophylactic effect with regard to spontaneous abortion. For AED therapy, folic acid supplementation should be part of the therapy of every pregnant epileptic woman, especially for those treated with VPA. The interaction between P450-inducing AEDs and folate metabolism may be clinically relevant and can be balanced by supplementation of small doses of folic acid [16]. Analysis for preterm delivery showed no significant numbers.

The results of this study support the recommendation that women of childbearing age treated with AEDs should receive folic acid supplementation. High dosages are not so clearly beneficial as expected. Prospective and larger cohort studies may show clearer results in the future.

■ **Conflict of interest** The authors declare no conflict of interest.

Table 4 Numbers and percentage of spontaneous abortions and preterm deliveries subdivided into those with folic acid supplementation and those with no supplementation. Odds ratios, 95 % CI and significance are calculated for pregnancies without supplementation and the event of a spontaneous abortion. Calculations were separately made for women with AED polytherapy, monotherapy and different AEDs in monotherapy. Out of these only the two major groups, VPA and CBZ, are shown here. Further numbers for VPA dosage higher than 1000 mg/d were separately analyzed

	Polytherapy	Monotherapy	VPA monotherapy	VPA > 1000 mg/d	CBZ monotherapy
Spontaneous abortion/ delivery (n)					
Without folic acid supplementation	2/52 (3.7 %)	28/140 (16.5 %)	15/43 (25.4 %)	1/20 (5 %)	11/56 (16 %)
With folic acid supplementation	1/29 (3.3 %)	8/120 (6.2 %)	1/43 (2.3 %)	1/24 (4 %)	6/53 (10 %)
Odds Ratio					
OR	1.1	2.9	14.5	1.15	1.7
95 % CI	0.1–12.5	1.3–6.8	1.8–115.8	0.7–19.8	0.6–5.0
Significance					
p	0.72	0.004	0.001	0.79	0.22
Preterm delivery/ delivery (n)					
Without folic acid supplementation	1/52 (1.9 %)	2/140 (1.4 %)	1/43 (2.3 %)	0/20 (0 %)	1/56 (1.7 %)
With folic acid supplementation	0/29 (0 %)	1/120 (0.8 %)	0/43 (0 %)	0/24 (0 %)	1/53 (1.8 %)

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