



Original Article

Effect of anti-epileptic drugs on first trimester screening test results

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ABSTRACT

Objective: To evaluate first trimester screening test parameters in epileptic patients using anti-epileptic drugs.

Materials and methods: We retrospectively evaluated first trimester screening test results of 23 epileptic pregnant women using anti-epileptic drugs with a control group consisting of 92 healthy pregnancies. The anti-epileptic drugs used in this study were carbamazepine, levatiracetam, valproic acid and lamotrigine. Single drug or multi-drug regimens were used according to the clinical conditions. Patients with any known chronic or acute disease and drug usage were excluded from the study. Comparisons were performed via Mann–Whitney U test.

Results: First trimester screening test biochemical markers were compared and maternal serum PAPP-A MoM values were found to be similar in study and control groups while β -hCG MoM values were significantly higher in pregnancies using epileptic drugs (p : 0.737 and p < 0.001, respectively).

Conclusion: Biochemical first trimester screening test results may be affected by anti-epileptic drug usage, which may lead to misinterpretation of the risk level. Thus, validation of MoM values should be necessary in order to obtain optimal results.

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Introduction

Epilepsy is the most common neurological disease worldwide. The prevalence of epilepsy during pregnancy is approximately 0.3–0.7% [1,2]. Although increased risk of adverse maternal and obstetric outcomes were reported in the literature, pregnancy progresses without complications in most cases [3,4]. Increased risk of congenital anomalies in these pregnancies is mostly associated with the use of antiepileptic drugs [5,6]. In addition, anti-epileptic drug use has an effect on hormone homeostasis [7]. Production and blood levels of β hCG, progesterone and estradiol were affected by the antiepileptic drugs valproic acid and levatiracetam. On the other hand, antiepileptic drugs also activate hepatic P-450 microsomal enzyme systems [8].

A combined test is one of the most common screening tests for aneuploidies. Multiples of median (MoM) levels of free beta-human chorionic gonadotropin (β -hCG) and maternal serum-related plasma protein-A (PAPP-A), ultrasonographic fetal nuchal

translucency measurement together with maternal age and gestational week were used in order to define a risk level for patients by means of a trivariate Gaussian algorithm [9]. Values $\geq 1/250$ –270 were regarded as high risk for aneuploidies [10,11]. An invasive prenatal diagnostic test was offered to patients with high risk screening test results [12]. Thus, optimal interpretation of the test result is crucial in order to prevent unnecessary interventions.

The aim of this study was to evaluate the effect of antiepileptic drugs on biochemical components of the first trimester combined screening test.

Materials and methods

In this retrospective study, we compared the biochemical components of first trimester aneuploidy screening test results (MoM values for β -hCG and PAPP-A) of pregnant women using anti-epileptic drugs (study group, $n = 23$) with pregnant women who were not epileptic and did not use any drugs (control group, $n = 92$). Maternal age, gravidity, parity and number of previous miscarriages, gestation at birth and birth weight were also compared between the groups. The anti-epileptic drugs used in this study were carbamazepine, levatiracetam, valproic acid and lamotrigine. Single drug or multi-drug regimens were used

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according to the clinical conditions. The required data were obtained from the electronic database of the Division of Perinatology, Hacettepe University. Informed consent was obtained from all patients included in the study.

Pregnant women in the control group had no known disease and had not taken any medication during the pregnancy. A first trimester aneuploidy screening test was applied to all pregnant women at 11–14 weeks of gestation. Maternal serum PAPP-A and free β -hCG MoM values were compared between the two groups.

The data were evaluated via descriptive statistics and Mann Whitney U test according to case numbers and data structure. A *p* value lesser than 0.05 was evaluated as significant. All statistical calculations were performed with the Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 23; SPSS Inc., Chicago, IL) statistical software package.

This retrospective study was approved by the Hacettepe University Ethics Committee (Number: GO 17/425).

Results

In this study, 23 pregnant women with epilepsy using anti-epileptic drugs were compared with 92 healthy pregnant women. Medical treatments and doses used during pregnancy are summarized in Table 1. The most commonly used medical therapy was carbamazepine alone for seven patients (30.4%). The other drugs used in our study group were levatiracetama, valproic acid and lamotrigine. Age, number of abortions, gestation at birth and neonatal birth weight were similar for both groups. Demographic characteristics and perinatal results are summarized in Table 2. On the other hand, when the first trimester screening test biochemical markers in maternal serum were compared between the two groups, maternal serum PAPP-A MoM values were not statistically significantly different, while β -hCG MoM values were significantly higher in those using epileptic drugs (*p*: 0.737 and *p* < 0.001, respectively). Additionally, from the results of evaluation of all patients included in the study, there was no chromosomal abnormality, neural tube defect or fetal death. Furthermore, we have compared different treatment modalities in terms of β -hCG MoM (Table 3). There was no statistically significant difference between different treatment modalities (*p*:0.197).

Discussion

Epilepsy is a common neurological disease in pregnant women, requiring close follow-up in the antenatal period [13]. In our study, we considered the effects of antiepileptic drug usage on first trimester screening test results. In some studies, antiepileptics, in particular valproic acid, have been reported to have impaired apoptotic and degenerative effects leading to reduced cell proliferation [14,15]. Some antiepileptic drugs were found to affect the production of β -hCG, progesterone and estradiol according to the previous literature [7]. Antiepileptic drugs have also been shown to

activate the hepatic P 450 microsomal enzyme system, which increases estrogen metabolism [8]. In the formation and differentiation of placental trophoblasts, the balance of apoptosis and β -hCG plays an important role [16]. For all these reasons, we speculated that the use of antiepileptic drugs might alter the values of biochemical components of screening tests and the results of the screening test may be misinterpreted. In addition, different forms of β -hCG were found to have different half lives resulting in different serum levels of that hormone [17,18]. This is also critical since metabolic changes according to anti-epileptic drug usage may influence the metabolism of β -hCG during early pregnancy. In our study, statistical analysis regarding to different treatment modalities demonstrated no significant difference in terms of β -hCG MoM values. However, we think that this lack of significance may be related to limited number of cases in certain groups and this finding must be confirmed by further series.

There are studies in the literature on the effects of autoimmune disorders on first trimester screening test results [19–22]. Heinig et al. indicated significantly higher levels of free β -hCG in the maternal serum of pregnant women with systemic lupus erythematosus in the first-trimester, however nuchal translucency and PAPP-A levels were not significantly different from the control group [19]. Turkcapar et al. demonstrated low levels of PAPP-A in pregnant women with Familial Mediterranean fever in the first trimester, but levels of free β -hCG in the first trimester were similar between women with Familial Mediterranean fever and healthy pregnant women [21]. Yilmaz et al. demonstrated that maternal serum PAPP-A, free β -hCG levels and nuchal translucency values in the first trimester, and uE3, total hCG and AFP levels in the second trimester were similar in pregnant women with Behçet's Disease in the absence of aneuploidy or neural tube defects compared with healthy pregnant women [22]. Thus, systemic inflammatory or metabolic alterations and/or toxic effects of the drugs may be influencing the MoM values of β -hCG, as we have demonstrated in our study. These results are also critical and must be kept in mind in the evaluation of first trimester screening results of epileptic patients using anti-epileptic drugs.

Anti-epileptic drug therapies may be safely continued during pregnancy and a change of treatment modality due to pregnancy is not recommended because of increased risks of seizure [23]. Dosing of medical treatment may be necessitated due to altered metabolism of drugs and changing levels of binding proteins [24]. Lower serum levels of drugs may end up with increased seizures or status epilepticus, which may be lethal. In our series, none of the patients had a status epilepticus with dosing of drugs by the neurology department.

In our series, we have concluded that MoM values of β -hCG are significantly higher compared to control group. This is an important finding as this may lead to misinterpretation of the screening results. Pregnancies with Down syndrome are associated with increased MoM values of β -hCG. Thus, patients using anti-epileptic drugs may be evaluated as high risk patients according to our

Table 1
Patients using antiepileptic drugs, doses and drug usage times.

	Number of Patients	Min-Max Dose	Duration of Treatment
Carbamazepine	7 (30.4%)	200–1200 mg/day	7–20 years
Levatiracetam	6 (26%)	500–1000 mg/day	8–19 years
Valproic Acid	6 (26%)	500–1000 mg/day	1–20 years
Lamotrigine	1 (4.3%)	300 mg/day	10 years
Combined Therapy	3 (12.9%)		
Valproic Acid + Levatiracetam	2 (8.6%)	1000 mg/day 1000 mg/day	9–13 years
Carbamazepine + Levatiracetam	1 (4.3%)	1200 mg/day 1000 mg/day	20 years

Table 2

Comparison of control group and epileptic patients with medical treatment in terms of obstetric history and combined screening test results.

	Control Group	Epileptic Patients with Medical Treatment	p
Age	29 (19–42)	28 (17–38)	0.465
Gravidity	2 (1–6)	2 (1–8)	0.030
Parity	1 (0–3)	1 (0–5)	0.001
Abortus	0 (0–3)	0 (0–6)	0.141
Living Child	1 (0–3)	1 (0–4)	0.001
Birthweek	38.2 (29.1–41)	38 (32.2–41.4)	0.216
Birthweight	3200 (1020–4290)	3075 (1380–4210)	0.309
hcG MoM	0.79 (0.22–1.84)	1.23 (0.65–2.66)	0.000
PAPP-A MoM	0.99 (0.26–4.13)	1.18 (0.49–2.34)	0.737

Statistically significant results were reported as bold.

Table 3Comparison of β -hCG MoM values according to antiepileptic drugs.

	β -hCG MoM
Carbamazepine	1.18 (0.67–1.65)
Levetiracetam	1.15 (0.81–2.45)
Valproic Acid	1.82 (1.21–2.66)
Lamotrigine	1.13
Combined Therapy	
Valproic Acid + Levetiracetam	0.69 (0.65–0.73)
Carbamazepine + Levetiracetam	1.24
p value	0.197

analysis and may necessitate invasive diagnostic tests for the confirmation of this situation. This is a critical concern, as the invasive diagnostic tests are associated with increased financial burden and early pregnancy losses. However, this is a retrospective study and our results must be confirmed by larger prospective series before changing our clinical approaches for this certain group of patients.

Limitations of this study were the relatively small sample size and the retrospective design. The other limitation was the heterogeneity of treatment modalities. On the other hand, to the best of our knowledge, this is the first study evaluating first trimester serum screening markers in epileptic pregnant women using anti-epileptic drugs.

In conclusion, biochemical first trimester screening test results may be affected by anti-epileptic drug usage, which may lead to misinterpretation of the risk level. Thus, validation of MoM values should be necessary in order to obtain optimal results.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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