

Article

Not peer-reviewed version

Impact of Antiepileptic Drug Use on Second-Trimester Screening Test Parameters in Pregnancy

[Melisa Golgelioglu](#)*, [Cigdem Akcabay](#), Gunes Seda Albayrak, [Selda Telo](#)

Posted Date: 28 May 2025

doi: 10.20944/preprints202505.2224.v1

Keywords: alpha-fetoprotein; fetal anomalies; human chorionic gonadotropin; teratogenicity; un-conjugated estriol



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

Impact of Antiepileptic Drug Use on Second-Trimester Screening Test Parameters in Pregnancy

Melisa Golgelioglu ^{1,*}, Cigdem Akcabay ², Gunes Seda Albayrak ³ and Selda Telo ⁴

¹ Yozgat City Hospital, Department of Obstetrics and Gynaecology, Yozgat, Turkey
² Firat University Facult of Medicine, Department of Obstetrics and Gynaecology, Elazig, Turkey
³ Yozgat Bozok University Faculty of Medicine, Department of Neurology, Yozgat, Turkey
⁴ Firat University Facult of Medicine, Biochemistry and Clinical Biochemistry, Elazig, Turkey
* Correspondence: melisatutar95@gmail.com

Abstract: *Background and Objectives:* Use of antiepileptic drugs (AEDs) during pregnancy is critical for seizure control in women with epilepsy but raises concerns regarding the use of these drugs and their possible effect on maternal serum biochemical markers used for second-trimester prenatal screening. The aim of this study was to assess the effect of AEDs on maternal serum alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) during serum biomarker analysis in second-trimester prenatal screening. *Materials and Methods:* This retrospective cohort study included 43 pregnant women using AEDs (levetiracetam, lamotrigine, carbamazepine, or combined therapy) and 43 matched controls without medication use. Groups were matched based on maternal age, gravidity, parity, abortion history, gestational age at testing, body mass index, and smoking status using propensity score matching. Serum AFP, uE3, and hCG levels measured between 15–20 weeks of gestation were compared between groups. *Results:* Pregnant women taking AEDs had significantly higher maternal serum AFP (1.34 ± 0.42 vs. 1.01 ± 0.31 MoM; $p < 0.001$) and uE3 (1.28 ± 0.39 vs. 1.05 ± 0.34 MoM; $p = 0.004$) compared to controls. However, hCG did not differ significantly between groups (1.07 ± 0.46 vs. 1.01 ± 0.42 MoM; $p = 0.523$). Regarding the AED subgroup (levetiracetam, lamotrigine, or carbamazepine), there were no significant differences in serum biomarkers ($p > 0.05$). *Conclusions:* The use of AEDs during pregnancy significantly alters second-trimester maternal serum biochemical markers, including our primary concerns, AFP and uE3, which could cause inaccurate interpretations of second-trimester prenatal screening. Clinicians should carefully consider maternal medication exposure when interpreting these biochemical markers in pregnant women with epilepsy to prevent misclassification of fetal risks and avoid unnecessary invasive procedures.

Keywords: alpha-fetoprotein; fetal anomalies; human chorionic gonadotropin; teratogenicity; unconjugated estriol

1. Introduction

Epilepsy is one of the most prevalent neurological diseases in women during pregnancy (0.3–0.7% prevalence worldwide) [1]. Antiepileptic drugs (AEDs) are frequently used to treat seizures during pregnancy, which presents a problem because of the known teratogenicity risks [2]. Uncontrolled seizures in pregnancy have been correlated with adverse obstetric outcomes, such as miscarriage, stillbirth, preterm delivery, and developmental delays in offspring level, which necessitates control of seizures [3]. Pregnancies complicated by epilepsy should require individualized prenatal management protocols to avoid maternal and fetal harm [4]. Given the complex relationship between maternal health and fetal risk, precise prenatal screening and accurate interpretation of results for women with epilepsy during pregnancy is essential. There remains a

critical area of research in clinical care regarding AED therapy that has implications on maternal-fetal health.

Maternal serum screening tests to screen for fetuses with aneuploidies and neural tube defects during the second trimester are now performed routinely. The tests routinely examine markers of fetal origin, with the aim of quantifying maternal serum biomarker concentrations that include alpha fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) [5]. The importance of these biomarker levels in maternal serum as potential indicators of fetal anomalies or genetic conditions and for assessing potential adverse maternal-fetal outcomes in pregnancy cannot be underestimated. This means that careful interpretation of these tests is important in clinical practice because they can inform important decisions regarding further diagnostic investigations with invasive diagnostic procedures and care options in pregnancy [6–8]. Misinterpretation of these biomarkers can lead to unnecessary procedures, increased maternal anxiety and distress, and the potential cost of additional health care [6–8]. Therefore, it is vital that clinical factors that may influence marker levels in serum are carefully scrutinized to ensure sound clinical decision-making.

The hypothesis underpinning this study is predicated upon increasing, although limited, evidence suggesting that AEDs can impact maternal serum biochemical marker concentrations via multiple mechanisms of action. First, AEDs can induce hepatic microsomal enzymes, specifically, the cytochrome P450 enzyme system, which is involved in the metabolism and clearance of hormones. Previous studies have shown that carbamazepine, valproic acid, and levetiracetam give rise to meaningful activation of hepatic enzymes [9,10]. The activation of hepatic enzymes may cause maternal serum concentrations of hormones such as AFP, uE3, and hCG to be altered. Second, direct effects of valproic acid and levetiracetam on hormone secretion from trophoblastic cells have been documented, which is further evidence of their potential impact on biochemical markers utilized for prenatal screening [11]. Despite these indications, clinical studies investigating the effects of AEDs on second-trimester maternal serum screening tests are limited in number, often methodologically heterogeneous, and involve relatively small sample sizes [12,13].

Thus, the current study's main focus is to determine if the use of AED has an impact on maternal serum biochemical marker levels in screening tests during the second trimester. This study aims to clarify these potential impacts to improve clinical interpretation of screening test results, reduce unnecessary invasive procedures, and optimize prenatal management for pregnant women with epilepsy.

2. Materials and Methods

2.1. Study Design

This study was designed as a retrospective cohort analysis conducted at the obstetrics and gynecology departments of three hospitals (two tertiary care centers and one secondary care center). Medical records of patients (who used antiepileptic drugs during pregnancy) were reviewed to evaluate the effects of these medications on second-trimester maternal serum screening test results. The study commenced after receiving approval from the Firat University Institutional Review Board (approval date: 01/11/2024, approval number: 28573). All procedures performed in this study adhered to the ethical standards of the institutional and national research committee, as well as the principles outlined in the Declaration of Helsinki for medical research involving human subjects.

2.2. Patient Selection

This study included pregnant women with epilepsy who attended our obstetrics and gynecology departments between January 2020 and September 2024. Pregnant women aged between 18 and 44 years, using antiepileptic drugs throughout pregnancy, and having second-trimester maternal serum screening test results available were included. Exclusion criteria for the epilepsy group were multiple pregnancies, chronic systemic diseases (such as diabetes mellitus, hypertension, or autoimmune disorders), known chronic hepatic disorders (e.g., chronic hepatitis, cirrhosis, primary biliary cholangitis), and pregnancies with incomplete medical records or unavailable serum screening

results. Isolated elevations of liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) were not considered exclusion criteria in the epilepsy group, as these elevations could be potentially related to antiepileptic drug use. Initially, medical records of 64 pregnant women with epilepsy were evaluated. Among these, 5 patients were excluded due to multiple pregnancies, 8 patients due to chronic systemic diseases (4 diabetes mellitus, 3 hypertension, 1 autoimmune disorder), 3 patients due to known chronic hepatic disorders, and 5 patients due to incomplete medical records or unavailable serum screening test results. After applying these inclusion and exclusion criteria, a total of 43 patients remained eligible and were included in the analysis. For patients using AEDs, the medication consistently used during at least the three months prior to the second-trimester maternal serum screening test was taken as the basis for the analysis.

The control group consisted of pregnant women who did not use any antiepileptic or other medications and who attended the obstetrics and gynecology departments of the same hospitals during the same period. Exclusion criteria for the control group were identical to those of the epilepsy group: multiple pregnancies, chronic systemic diseases (e.g., diabetes mellitus, hypertension, autoimmune disorders), known chronic hepatic disorders (e.g., chronic hepatitis, cirrhosis, primary biliary cholangitis), elevated liver enzymes (ALT or AST greater than two times the upper limit of normal), and incomplete medical records or unavailable serum screening results. Control patients were matched to patients in the epilepsy group using propensity score matching with respect to age, gravidity, parity, abortion history, gestational age at testing, BMI, and smoking status [14]. If a patient had more than one candidate to match as a control to a patient from the epilepsy group, the candidate with the most similar propensity score to the reference patient was chosen to ensure matched pairs had the least differences [14]. If multiple control candidates were available for matching with an individual patient from the epilepsy group, the patient with the closest propensity score was selected, ensuring minimal differences between matched pairs. Following propensity score matching, a total of 43 patients were included in each group.

2.3. Data Collection

Data were collected retrospectively from electronic medical records stored in the hospital information system and patient files at the obstetrics and gynecology departments of the participating hospitals. Demographic data such as maternal age, gravidity, parity, abortion history, smoking status, and BMI were recorded. Clinical data, including gestational age at the time of second-trimester serum screening (between 15 and 20 weeks of pregnancy), antiepileptic drug type and dosage, duration of drug use, and maternal systemic diseases, were also obtained from the records. Additionally, second-trimester maternal serum screening test results—including maternal serum AFP, uE3, and hCG—were extracted from the laboratory database. To ensure data accuracy and completeness, all collected data were independently verified by two investigators, and discrepancies were resolved by consensus.

2.4. Biochemical Analysis

Maternal serum biochemical marker levels were measured as part of routine second-trimester maternal serum screening tests at the laboratory departments of the participating hospitals. Serum samples were collected from pregnant women between 15 and 20 weeks of gestation. Biochemical markers including AFP, uE3, and hCG were quantitatively measured using a commercially available chemiluminescence immunoassay method (Roche Cobas® analyzer, Roche Diagnostics, Mannheim, Germany), in accordance with the manufacturer's protocols. Marker levels were expressed as multiples of the median (MoM), adjusted for gestational age, maternal weight, and smoking status. Routine quality control procedures, including internal and external quality assurance measures, were regularly performed.

2.5. Statistical Analysis

Descriptive statistics were presented as mean $\pm$ standard deviation for continuous variables and as frequencies and percentages for categorical variables. The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons between the epilepsy group and the control group for continuous variables were performed using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The chi-square test or Fisher's exact test was used for categorical variables, where appropriate. Comparisons among antiepileptic drug subgroups (lamotrigine, levetiracetam, carbamazepine) were performed using one-way ANOVA for normally distributed data and the Kruskal-Wallis test for non-normally distributed data. To ensure comparability between the epilepsy and control groups, propensity score matching was performed based on age, gravidity, parity, abortion history, gestational age at testing, BMI, and smoking status. Matching adequacy was evaluated by comparing standardized differences in matching variables between the two groups, with differences below 0.1 considered acceptable. A p-value of less than 0.05 was considered statistically significant for all analyses. Statistical analyses were performed using SPSS software (Version 27.0, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Propensity Score Matching Results

Propensity score matching was successful way to balance the groups. The standardized differences for all matching variables were reduced to below 0.1 after matching, suggesting the epilepsy and control groups had similar demographic and clinical characteristics (Table 1).

Table 1. Standardized differences for variables before and after propensity score matching.

Variables	Standardized Difference (Before Matching)	Standardized Difference (After Matching)
Maternal age	0.25	0.03
Gravidity	0.21	0.02
Parity	0.19	0.04
Abortion history	0.15	0.01
Gestational age at testing	0.22	0.03
BMI	0.31	0.05
Smoking status	0.17	0.00

BMI: Body mass index, Standardized difference values less than 0.1 indicate well-balanced variables between groups after matching.

3.2. Demographic and Clinical Characteristics

The final analysis included a total of 86 pregnant women (43 in the AED group and 43 in the control group). Demographic and clinical characteristics of the two groups are presented in Table 2. Both groups were similar regarding maternal age, gravidity, parity, abortion history, gestational age at the time of serum screening, BMI, and smoking status (all $p > 0.05$), indicating successful matching through propensity score matching (all standardized differences < 0.1).

Table 2. Demographic and clinical characteristics of the antiepileptic drug and control groups.

Variables	AED group (n = 43)	Control group (n = 43)	p-value
Maternal age (years)	29.6 $\pm$ 5.2	29.2 $\pm$ 4.9	0.712
Gravidity	2.4 $\pm$ 1.3	2.3 $\pm$ 1.4	0.825
Parity	1.2 $\pm$ 0.8	1.1 $\pm$ 0.7	0.615
Abortion history	0.3 $\pm$ 0.6	0.3 $\pm$ 0.5	0.893

Variables	AED group (n = 43)	Control group (n = 43)	p-value
Gestational age at testing (weeks)	17.6 ± 1.2	17.8 ± 1.1	0.423
BMI (kg/m ²)	26.1 ± 4.0	25.7 ± 3.8	0.648
Smoking status, n (%)			1.000
- Smoker	6 (14.0%)	6 (14.0%)	
- Non-smoker	37 (86.0%)	37 (86.0%)	

AED: Antiepileptic drug, BMI: Body mass index, data presented as number (%) or mean ± standard deviation (SD).

3.3. Antiepileptic Drug Types and Daily Doses in the Study Group

The types, frequencies, and average daily doses of AEDs used by the participants in the AED group are summarized in Table 3. The frequency of AED use was as follows: levetiracetam (41.9%), lamotrigine (37.2%), carbamazepine (16.3%), and combined lamotrigine + levetiracetam (4.7%).

Table 3. Types, frequencies, and daily doses of antiepileptic drugs.

Antiepileptic Drug	Patients, n (%)	Daily Dose, mean ± SD (mg/day)	Dose range (mg/day)
Levetiracetam	18 (41.9%)	1380 ± 510	500 – 3000
Lamotrigine	16 (37.2%)	210 ± 85	50 – 400
Carbamazepine	7 (16.3%)	640 ± 210	400 – 1200
Lamotrigine + Levetiracetam (combined)	2 (4.7%)	Lamotrigine: 175 ± 35	150 – 200
		Levetiracetam: 1250 ± 350	900 – 1600

Data presented as number (%) or mean ± standard deviation (SD).

3.4. Comparison of Second-Trimester Maternal Serum Biochemical Markers

Second-trimester maternal serum biochemical marker levels (AFP, uE3, and hCG) in the AED and control groups are presented in Table 4. Maternal serum AFP (1.34 ± 0.42 vs. 1.01 ± 0.31 MoM; p < 0.001) and uE3 (1.28 ± 0.39 vs. 1.05 ± 0.34 MoM; p = 0.004) levels were significantly higher in the AED group compared to the control group. No statistically significant difference was observed between groups for maternal serum hCG levels (1.07 ± 0.46 vs. 1.01 ± 0.42 MoM; p = 0.523).

Table 4. Second-trimester maternal serum biochemical marker levels.

Marker (MoM)	AED Group (n=43)	Control Group (n=43)	p-value
AFP	1.34 ± 0.42	1.01 ± 0.31	<0.001
uE3	1.28 ± 0.39	1.05 ± 0.34	0.004
hCG	1.07 ± 0.46	1.01 ± 0.42	0.523

AED: Antiepileptic drug, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, MoM: Multiples of median, uE3: Unconjugated estriol, data presented as mean ± standard deviation (SD).

3.5. Comparison of Unconjugated Estriol and Alpha-Fetoprotein Values According to Antiepileptic Drug Type

Maternal serum biochemical marker levels according to the type of AED used are summarized in Table 5. No significant differences were observed between the lamotrigine, levetiracetam, and carbamazepine groups regarding maternal serum AFP and uE3 levels (all p > 0.05).

Table 5. Maternal serum unconjugated estriol and alpha-fetoprotein levels according to antiepileptic drug type.

Marker (MoM)	Lamotrigine (n=16)	Levetiracetam (n=18)	Carbamazepine (n=7)	p-value
AFP	1.29 ± 0.34	1.32 ± 0.38	1.39 ± 0.37	0.662
uE3	1.23 ± 0.33	1.27 ± 0.35	1.31 ± 0.36	0.721

AFP: Alpha-fetoprotein, uE3: Unconjugated estriol, MoM: Multiples of median, data presented as mean ± standard deviation (SD).

4. Discussion

The most important findings of this study were that maternal serum AFP and uE3 levels were significantly increased in pregnant women using AEDs compared to other pregnant women who did not used any medication. However, hCG did not show a significant difference between groups. Additionally, no evident differences in AFP and uE3 levels were detectable between the different AED subtypes in the investigation.

Our results were consistent with previous studies having increased maternal serum AFP and uE3 levels regarding the use of AEDs in pregnancy [12,13]. In fact, Besimoglu et al. [12] reported significantly increased second trimester median serum AFP and uE3 levels among pregnant women taking AEDs relative to their cohort controls, which is precisely the same as we found. Similarly, Oksuzoglu et al. [13] based on information from their study suggested that second trimester biochemical markers levels were higher among the pregnant women using AEDs in their cohort. This reinforces the findings of our study related to the influence of taking AEDs on the maternal prenatal screening and outcomes data, although both previous studies included groups of heterogeneous patients, we used propensity score matching to create well-balanced groups for study comparison, to help control for confounding variables and provide more sound findings and conclusions.

The elevated maternal serum AFP and uE3 levels observed in our study may be explained by several pharmacological and physiological mechanisms associated with AED use. Primarily, certain AEDs, especially carbamazepine, are known to induce hepatic microsomal enzymes, particularly the cytochrome P450 enzyme system, which plays a critical role in hormone metabolism and clearance [9,11]. Increased hepatic enzyme activity could accelerate hormone clearance and trigger compensatory increases in AFP and uE3 synthesis. Although lamotrigine and levetiracetam are generally recognized as weaker enzyme inducers compared to carbamazepine, these AEDs might still influence hormonal pathways through alternative mechanisms, including modulation of placental transport functions, indirect effects on maternal liver metabolism, or increased renal clearance during pregnancy due to enhanced renal blood flow and glomerular filtration rate [15,16]. The absence of significant changes in hCG levels in our study aligns with previous findings [12,13]. This could be due to hCG secretion being less susceptible to hepatic enzyme induction and primarily regulated by placental trophoblastic activity, differing mechanistically from steroid hormone synthesis pathways. Similar interpretations were provided by Besimoglu et al. and Oksuzoglu et al., who suggested that different hormonal markers exhibit variable sensitivity to the effects of AEDs, reflecting diverse metabolic and physiological pathways [12,13]. We believe our findings reflect these multifaceted pharmacological and physiological mechanisms.

In this study, demographic and clinical characteristics were effectively balanced between the AED and control groups, as demonstrated by standardized differences below 0.1 after propensity score matching. Specifically, critical confounding factors, such as maternal age, gravidity, parity, abortion history, gestational age at testing, BMI, and smoking status, were carefully matched to ensure comparability between groups. Previous studies indicate that these demographic and clinical variables can significantly affect maternal serum biochemical marker levels during pregnancy [17–19]. Therefore, achieving balanced groups was essential to confidently attribute the observed differences in biochemical markers primarily to AED usage rather than confounding variables.

In the present study, levetiracetam (41.9%) and lamotrigine (37.2%) were the most commonly prescribed AEDs, followed by carbamazepine (16.3%), while a small proportion (4.7%) used combined therapy (lamotrigine and levetiracetam). These findings align well with current clinical guidelines, which generally recommend levetiracetam and lamotrigine as first-line AED treatments during pregnancy due to their favorable safety profiles and lower teratogenic risks compared to older AEDs such as valproic acid or carbamazepine [20,21]. Notably, we observed that none of the participants used valproic acid, which likely reflects recent clinical trends advocating against its use during pregnancy due to well-established teratogenic effects [22]. Additionally, consistent with our study protocol, we considered only the AED that was consistently used for at least three months before the second-trimester screening test, thus preventing potential confounding effects resulting from medication changes during pregnancy. Furthermore, the average daily doses of these medications in our study were within therapeutic ranges commonly reported in the literature for pregnant patients [23]. A recent review similarly emphasized that levetiracetam and lamotrigine are preferred in pregnancy due to their stable pharmacokinetic properties, minimal drug interactions, and reduced impact on hepatic metabolism [21]. Thus, the distribution and dosing patterns of AEDs observed in our study cohort reflect current clinical practice and guidelines for epilepsy management during pregnancy.

Our subgroup analysis did not demonstrate significant differences in maternal serum AFP and uE3 levels among the different AED types (lamotrigine, levetiracetam, carbamazepine). Although carbamazepine is recognized as a stronger inducer of hepatic enzymes compared to lamotrigine and levetiracetam [2,9], the absence of significant differences in our study is likely attributable to the limited sample sizes within each subgroup. Similar results were reported in previous studies [12,13].

The findings of this study carry important clinical implications for prenatal care management in pregnant women using AEDs. Elevated maternal serum AFP and uE3 levels among AED users highlight the need for cautious interpretation of second-trimester maternal serum screening results to avoid potential misclassification of fetal risk. Clinicians should be aware of possible false-positive results in these patients, which could lead to unnecessary anxiety, invasive diagnostic procedures, and increased healthcare costs. Therefore, it is essential to incorporate maternal medication history into risk assessment algorithms, potentially adjusting reference ranges or using individualized risk calculations. Ultimately, recognizing the influence of AED therapy on maternal serum biochemical markers can enhance the accuracy of prenatal screening outcomes and optimize prenatal counseling strategies for pregnant women with epilepsy.

One of the primary strengths of our study is the use of rigorous propensity score matching, which significantly enhanced the robustness, internal validity, and reliability of our observed associations by ensuring balanced demographic and clinical characteristics between groups. Moreover, our study included a clearly defined AED-exposed population with consistent medication use for at least three months prior to the second-trimester screening test, minimizing potential confounding effects from medication changes during pregnancy. Additionally, the multicentric design involving both tertiary and secondary care centers increased the generalizability of our findings. Lastly, our study provides detailed information on the types and dosages of AEDs used, reflecting current clinical practices and enhancing the relevance of our results for clinical settings.

Our study has several limitations that need to be considered when interpreting the findings. First, the retrospective nature of our research inherently limits the control over data quality and completeness. Second, despite careful matching, the relatively small sample size may have restricted the statistical power to detect subtle but clinically meaningful differences, especially within individual AED subgroups. Furthermore, the limited numbers within each AED type subgroup prevented meaningful analyses of potential dose-dependent effects of AEDs on maternal serum biochemical markers. Additionally, the combined therapy subgroup (lamotrigine + levetiracetam) could not be included in subgroup analyses due to an insufficient number of patients. Lastly, the study lacked long-term neonatal outcome data, limiting our ability to correlate biochemical marker changes directly with clinical pregnancy outcomes or fetal complications.

Future studies should aim to address the limitations identified in our research by utilizing larger, prospective cohorts to validate these findings and to enhance statistical power, especially for subgroup analyses. Additionally, research designed to specifically investigate dose-dependent effects of individual AEDs on maternal biochemical marker levels could significantly contribute to our understanding of medication-specific risks during pregnancy. Moreover, longitudinal studies assessing not only biochemical markers but also detailed neonatal and long-term neurodevelopmental outcomes would provide more comprehensive insights into the clinical relevance of these biochemical alterations. Ultimately, such research could help refine prenatal screening guidelines and optimize management strategies for pregnant women with epilepsy.

5. Conclusions

In conclusion, maternal use of antiepileptic drugs during pregnancy significantly elevates second-trimester maternal serum AFP and uE3 levels, potentially impacting the interpretation of prenatal screening tests. Clinicians should carefully consider medication exposure when evaluating these biochemical markers in pregnant women with epilepsy to prevent misclassification of fetal risks and avoid unnecessary invasive procedures. Future larger-scale, prospective studies are needed to confirm these findings and to further refine prenatal management strategies in AED-exposed pregnancies.

Author Contributions: Conceptualization, M.G. and S.B.K.; methodology, G.S.A.; software, G.S.A.; validation, S.B.K., M.G. and C.A.; formal analysis, G.S.A.; investigation, M.G.; resources, C.A.; data curation, G.S.A.; writing—original draft preparation, M.G.; writing—review and editing, S.B.K.; visualization, E.C.K.; supervision, E.C.K.; project administration, S.B.K.; funding acquisition, M.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Firat University (protocol code: 28573 date: 01/11/2024).

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
hCG	Human chorionic gonadotropin
CPR	Cerebroplacental Ratio
MoM	Multiples of median
AC	Abdominal Circumference
BMI	Body Mass Index
uE3	Unconjugated estriol

References

1. Fiest, K.M.; Sauro, K.M.; Wiebe, S.; Patten, S.B.; Kwon, C.S.; Dykeman, J.; Pringsheim, T.; Lorenzetti, D.; Jetté, N. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology*. **2017**, *88*, 296–303.
2. Tomson, T.; Battino, D.; Bonizzoni, E.; Craig, J.; Lindhout, D.; Sabers, A.; Perucca, E. Teratogenicity of antiepileptic drugs. *Curr. Opin. Neurol.* **2019**, *32*, 246–252.
3. Voinescu, P.E.; Pennell, P.B. Management of epilepsy during pregnancy. *Expert Rev. Neurother.* **2015**, *15*, 1171–1187.
4. Harden, C.L.; Hopp, J.; Ting, T.Y.; Pennell, P.B.; French, J.A.; Hauser, W.A.; Wiebe, S.; Gronseth, G.S.; Thurman, D.; Meador, K.J.; et al. Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency. *Epilepsia*. **2009**, *50*, 1229–1236.
5. Alldred, S.K.; Deeks, J.J.; Guo, B.; Neilson, J.P.; Alfirevic, Z. Second trimester serum tests for Down's Syndrome screening. *Cochrane Database Syst. Rev.* **2012**, *2012*, CD009925.
6. Zhang, X.; Wang, W.; He, F.; Zhong, K.; Yuan, S.; Wang, Z. Proficiency testing of maternal serum prenatal screening in second trimester in China, 2015. *Biochem. Med (Zagreb)*. **2017**, *27*, 114–121.
7. Yazdani, S.; Rouholahnejad, R.; Asnafi, N.; Sharbatdaran, M.; Zakershob, M.; Bouzari, Z. Correlation of pregnancy outcome with quadruple screening test at second trimester. *Med. J. Islam. Repub. Iran*. **2015**, *29*, 281.
8. Pranpanus, S.; Kor-Anantakul, O.; Suntharasaj, T.; Suwanrath, C.; Hanprasertpong, T.; Pruksanusak, N.; Petpichetchian, C.; Suksai, M.; Chainarong, N.; Sawaddisan, R. Ethnic-specific reference range affects the efficacy of quadruple test as a universal screening for Down syndrome in a developing country. *PLoS One*. **2021**, *16*, e0251381.
9. Sugiyama, I.; Murayama, N.; Kuroki, A.; Kota, J.; Iwano, S.; Yamazaki, H.; Hirota, T. Evaluation of cytochrome P450 inductions by anti-epileptic drug oxcarbazepine, 10-hydroxyoxcarbazepine, and carbamazepine using human hepatocytes and HepaRG cells. *Xenobiotica*. **2016**, *46*, 765–774.
10. Kuchnowska, D.; Stachura, A.; Kosinski, P.; Gawlak, M.; Wegrzyn, P. Accuracy of estimated fetal weight assessment in fetuses with congenital diaphragmatic hernia – Is the Hadlock formula a reliable tool? *J. Clin. Med.* **2024**, *13*, 3392.
11. Chen, Y.; Wang, Y.; Zhao, W.; Ma, X.; Qu, X.; Liang, H.; Liu, X.; Wang, X.; Zhang, Y.; Gao, Y.; et al. Antiepileptic drugs carbamazepine and valproic acid mediate transcriptional activation of CYP1A1 via aryl hydrocarbon receptor and regulation of estrogen metabolism. *Toxicol. Lett.* **2017**, *271*, 30–39.
12. Besimoglu, B.; Öcal, F.D.; Sinaci, S.; Atalay, A.; Tanaçan, A.; Şahin, D. Effect of antiepileptic drugs on serum biochemical marker levels of first and second trimester screening tests. *J. Obstet. Gynaecol. Res.* **2022**, *48*, 1607–1612.
13. Oksuzoglu, A.; Ustun, Y.E.; Aktulay, A.; Yoruk, O.; Seckin, B.; Danisman, N. First and second trimester biochemical markers in maternal epilepsy: A case-control study. *Fetal Pediatr. Pathol.* **2018**, *37*, 319–325.
14. Austin, P.C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav. Res.* **2011**, *46*, 399–424.
15. Pennell, P.B.; Newport, D.J.; Stowe, Z.N.; Helters, S.L.; Montgomery, J.Q.; Henry, T.R. The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology*. **2004**, *62*, 292–295.
16. Tomson, T.; Palm, R.; Källén, K.; Ben-Menachem, E.; Söderfeldt, B.; Danielsson, B.; Johansson, R.; Luef, G.; Öhman, I. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia*. **2007**, *48*, 1111–1116.
17. Banhid, F.; Acs, N.; Puho, E.H.; Czeizel, A.E. Maternal cigarette smoking during pregnancy and risk of congenital abnormalities in offspring. *Int. J. Epidemiol.* **2011**, *40*, 145–161.
18. Spencer, K. The influence of maternal weight on maternal serum biochemical marker concentrations in the second trimester. *Prenat. Diagn.* **2011**, *31*, 362–365.
19. Huang, T.; Hoffman, B.; Meschino, W.; Kingdom, J.; Okun, N. Prediction of adverse pregnancy outcomes by combinations of first and second trimester biochemistry markers used in maternal serum screening. *Prenat. Diagn.* **2010**, *30*, 471–477.

20. Pack, A.M.; Oskoui, M.; Williams Roberson, S.; Johnson, E.L.; Voinescu, P.E.; Holmes, L.B.; Meador, K.J.; Patel, A.D.; Harden, C.L.; Pennell, P.B.; et al. Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication: Practice Guideline From the AAN, AES, and SMFM. *Neurology*. **2024**, *102*, e209279.
21. Meador, K.J.; Pennell, P.B.; Harden, C.L.; Gordon, J.C.; Tomson, T.; Kaplan, P.W.; Holmes, G.L.; French, J.A.; Hauser, W.A.; Wells, E.; et al. Practice guideline update summary: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* **2018**, *90*, e1664–e1672.
22. Macfarlane, A.; Greenhalgh, T. Sodium valproate in pregnancy: What are the risks and should we use a shared decision-making approach? *BMC Pregnancy Childbirth*. **2018**, *18*, 200-211.
23. Bromley, R.L.; Weston, J.; Marson, A.G. Monotherapy treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child. *Cochrane Database Syst. Rev.* **2014**, 2014, CD010224.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.