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ORIGINAL ARTICLE

# Neurobehavioral Outcomes of Children with Antenatal Exposure to Antiseizure Medications

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## Abstract

**Objectives** To evaluate the effect of antiepileptic medications prescribed to mothers during pregnancy on the development and behavior of children.

**Methods** From the Kerala Registry of Epilepsy and Pregnancy, 98 children between the ages of 1½ to 2½ y were consecutively chosen. Children of mothers who did not have epilepsy during pregnancy and not exposed to antiseizure medications (ASMs) antenatally were selected as comparator group. Developmental assessment of the children was performed using Developmental Assessment Scale for Indian Infants (DASII) and Receptive–Expressive Emergent Language Scale (REELS). Behavior outcomes were assessed using Child Behavior Checklist.

**Results** A significant delay in expressive language skills was seen in children exposed to antiseizure medication with an odds ratio of 2.539 (95% CI 1.10, 5.85, $P=0.026$). A delay in expressive language skills was seen in polytherapy with clobazam (odds ratio 6.83; 95% CI 2.17, 21.56, $P<0.001$). Also, delay was seen in receptive language skills in the same polytherapy group (odds ratio of 7.333; 95% CI 2.16, 24.92, $P<0.001$). There were no statistically significant differences between study and comparative groups in motor and mental quotient domains and behavioral outcomes.

**Conclusions** The finding of speech delay in children exposed to ASMs is significant since individuals with a history of childhood speech or language disorders may experience long-term difficulties in mental health, social well-being, and academic outcomes.

**Keywords** Antiepileptic medications · Neurodevelopment · Behavior problems · Speech delay · Autism spectrum disorder

## Introduction

*In utero* exposure to antiepileptic agents can cause poor neurodevelopmental outcomes, but the risk must be weighed against potentially serious risks that seizures during pregnancy can cause to both mother and fetus [1]. Seizures during pregnancy can cause trauma to the mother and is a non-obstetric cause for fetal demise (intracranial hemorrhage, decreased fetal heart rate, premature delivery, pregnancy loss) [2]. Antiepileptic drug (AED) use during pregnancy causes a two- to three-fold increased risk of major congenital malformations when compared with the general population [3], especially when exposed to more than one AED in pregnancy. Children born to mothers with epilepsy have been found to have an increased risk of developmental delay and cognitive impairments [4]. The present study aims to evaluate the effect of antiepileptic medications on the development, speech –language, and behavior outcome of children born to mothers with epilepsy during pregnancy, assessed between 1½ to 2½ y. Among the antiepileptic drugs, valproate (VPA) is found to be associated with significant harm to the unborn baby if taken by the mother during pregnancy. Epidemiological studies show that VPA is linked with a significant risk of birth defects (around 10 in 100 babies compared with 2–3 in 100 babies in the general population) and developmental disorders (about 30–40 children in every 100 may have developmental problems including delays in early development such as talking and walking later, lower

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intellectual abilities, poor language skills and memory problems) [4]. In a systematic review, twenty-nine cohort studies involving 5100 children of women who took AEDs were included. Out of all neurological outcomes and treatments compared with control, VPA alone or along with another AED was found to be associated with the greatest odds of adverse development. Oxcarbazepine and lamotrigine (LTG) were associated with increased occurrence of autism [2]. Cognitive and behavioral functioning of children of mothers with epilepsy has been less well studied in Indian setting. A review of previous literature on neurodevelopmental outcomes in children of mothers receiving antiseizure medications has been added as Table 1.

## Material and Methods

From the Kerala Registry of Epilepsy and Pregnancy (KREP), 98 children between the ages of 1½ to 2½ y were consecutively chosen. This study was a cross-sectional study. For assessing the difference in outcome between children born to mothers with epilepsy during pregnancy and children born to mothers with no epilepsy during pregnancy, a comparator group was also selected for the study. The comparative group was chosen by convenience sampling from Child Development Centre which is a government aided tertiary care centre in South Kerala dealing with neurodevelopmental follow up and neurodevelopmental disorders (NDDs). The comparative group included 50 children. Children between the ages of 1½ to 2½ y with no risk for NDDs (referred children from immunization clinic for the study) and those with mild risk for NDDs (classified according to the NNF criteria [13]) were consecutively selected. Mothers of children in the comparator group did not have epilepsy during pregnancy and they were not exposed to antiseizure medications (ASMs) antenatally. Children with any history of meningitis, encephalitis or head trauma were excluded from the study (Fig. 1). The selected children did not have pre-existing seizure disorder or any known neurodegenerative/ neurometabolic disorder. The socio-demographic details were collected from both the study and comparative groups. The anti-seizure medications history was collected from the KREP registry.

Developmental assessment of the children was performed using Developmental Assessment Scale for Indian Infants (DASII) [14] which gives the mental age and motor age. DASII is a standardized developmental tool which is an Indian adaptation of Bayley Scale of Infant Development (globally accepted gold standard). The mental and motor development quotient (DQ) of less than 85 was considered as impairment and above 85 was taken as normal. DASII was administered by trained senior developmental therapist.

Speech and language skills were assessed using Receptive–Expressive Emergent Language Scale (REELS) (birth-36 mo). The two subtests- receptive language and expressive language can be converted into quotients. A quotient of $<70$ was considered as delay and a quotient $>70$ was considered as normal [15].

The behavior of the children was assessed using the Checklist for Behavior in Children (CBCL) [16]. The CBCL/1.5-5 gives ratings of 99 problem items. The items are scored on the following syndrome scales: Emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behavior, and sleep problems. Items are also scored on the following Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) oriented scales: Depressive problems, anxiety problems, autism spectrum problems, attention deficit/hyperactivity problems and oppositional defiant problems. The CBCL was administered to all the children by the principal investigator. The behavioral, speech and developmental assessments were blinded, and the examiners did not know the status of children as cases or comparative group.

The main outcome variables of the study included; Developmental outcomes using DASII mental DQ and motor DQ, REELS expressive language quotient (ELQ) and receptive language quotient (RLQ) and Behavioral outcomes- DSM-5 for autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety, depression and Oppositional Defiant Disorder (ODD) (CBCL) (Fig. 2). The outcome variables were compared in the participants with the comparative group using Chi squared test and Fisher exact test. The data was analysed using SPSS version 26.0.

## Results

There were 97 children in the study group. The mean participant age was 24.7 mo (standard deviation, 2.91). Percentage of boys was 52.6% and of girls was 47.4%. There were 50 children in the comparative group. The mean comparative group age was 24.8 mo (standard deviation, 5.3). The percentage of boys was 44% (22) and of girls was 56% (28). Most common anti-seizure medications used were carbamazepine (CBZ), levetiracetam (LEV), sodium valproate and clobazam. Sixty-seven mothers were on monotherapy and 30 were on polytherapy. Of the 97 study group participants, REELS was completed for 91 participants and DASII test for 92 participants. All children in the comparative group completed both the tests.

Children with impaired mental and motor development, and language functions were selected. The difference in proportion between comparison and control groups was assessed using odds ratio. The study group had higher odds for expressive language skills when compared to the

**Table 1** Summary of studies assessing cognitive and behavioral outcomes of children of mothers receiving antiseizure medications

| Author (Year of publication) | Study setting | Study design | Neurodevelopmental outcomes studied | Age at observation | Major findings |
|---|---|---|---|---|---|
| Peron et al. (2024) [5] | Comparative studies from any setting evaluating the incidence of neurodevelopmental outcomes following exposure to lamotrigine monotherapy during pregnancy | Systematic review and meta-analysis | Neurodevelopmental disorders (NDD), language disorders or delay, psychomotor developmental disorders or delay, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cognitive developmental delay, learning disorders | < 3 y, 3–6 y and > 6 y | An increased risk of psychomotor developmental disorders or delay and cognitive developmental delay was observed in children aged < 3 y who were exposed to lamotrigine monotherapy prenatally. |
| Meador et al. (2023) [6] | Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study conducted at 20 specialty epilepsy centres in the USA | Prospective cohort | Neuropsychological outcomes- verbal index scores, secondary cognitive outcomes | 3 y | There was no statistically significant difference in verbal index scores between children who are exposed to anti-seizure medications. The overall cognitive outcomes of children exposed to levetiracetam were not different from those of children whose mothers did not have epilepsy. |
| Bjørk et al. (2022) [7] | Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden | Cohort study | Autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder | 8 y | There is increased risk for ASD and ID among children exposed to sodium valproate. Compared to children who were not exposed to clonazepam, carbamazepine, or oxcarbazepine during pregnancy, children who are exposed were more likely to have ASD and ID. |
| Meador et al. (2021) [8] | Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study conducted at 20 specialty epilepsy centres in the USA | Prospective cohort | Language domain score from the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) | 2 y | There was no association with language outcomes and children who were exposed to anti-seizure medications. Lower scores in the motor domain of BSID, was associated with higher anti-seizure medication level at third trimester of pregnancy. |

**Table 1** (continued)

| Author (Year of publication) | Study setting | Study design | Neurodevelopmental outcomes studied | Age at observation | Major findings |
|---|---|---|---|---|---|
| Blotière et al. (2020) [9] | Live births from January 2011 to December 2014 in France | Cohort study | NDD, pervasive developmental disorders (PDD) and mental retardation (MR) | The median follow-up age was 3.7 y. | Valproic acid (VPA) was associated with increased risk for NDDs. Exposure to valproate was associated with increased risks of NDDs, PDD and MR. |
| Daugaard et al. (2020) [10] | Singletons births in Denmark between January 1, 1997, and December 31, 2011 | Cohort study | ID, ID with delayed childhood milestones | Median age of 10.1 y at final follow-up. | Children of women who used valproate during pregnancy had a higher risk of ID and ID with delayed childhood milestones compared to children not exposed to valproate prenatally. |
| Richards et al. (2019) [11] | New Zealand | Retrospective cohort | Neurodevelopmental outcomes assessed using Before School Check (B4SC), Parental Evaluation of Developmental Status (PEDS) questionnaire and Strengths and Difficulties Questionnaire (SDQ). | 4 y | Parents reported a higher likelihood of emotional and behavioral development difficulties among children exposed to sodium valproate and lamotrigine antenatally. Prenatal exposure to AED polytherapy was associated with the highest risk of abnormal SDQ-Parent completed (SDQP) scores. |
| Huber-Mollema et al. (2019) [12] | Netherland | Prospective observational study | Behavioral outcomes assessed using Child Behavior Checklist and the Social Emotional Questionnaire | Mean age 6.7 y | Among the AED exposure groups, there was high proportion of children with behavior problems; valproate-exposed children had significantly more social problems than those exposed to lamotrigine. |

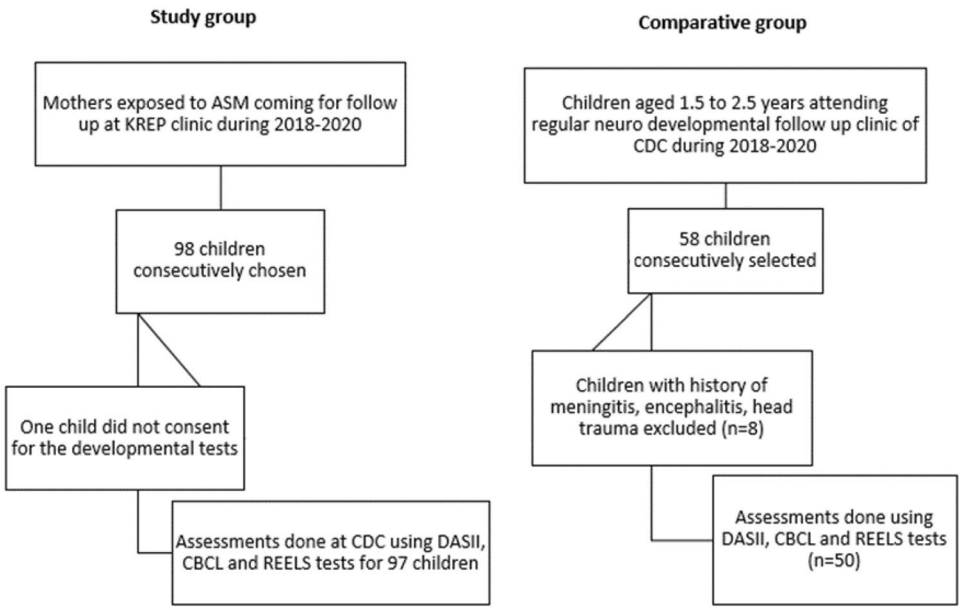


**Fig. 1** Selection criteria of patients. *ASMs* Antiseizure medications, *CBCL* Checklist for Behavior in Children, *CDC* Child Development Centre, *DASII* Developmental Assessment Scale for Indian Infants, *KREP* Kerala Registry of Epilepsy and Pregnancy, *REELS* Receptive–Expressive Emergent Language Scale

comparative group (OR: 2.54; 95% CI: 1.10, 5.85) (Table 2). There were no statistically significant differences in motor and mental quotients.

Statistically significant delay in expressive and receptive language skills was seen in polytherapy with clobazam [OR: 6.83, 95% CI: (2.17, 21.57)] and [OR: 7.33, 95% CI: (2.158, 24.915)] respectively. Individual polytherapy associations of clobazam with different ASMs like CBZ, VPA and LEV were not assessed as the numbers were small. Clobazam is rarely used as monotherapy as it is not the first drug of choice for most types of seizures. In this study, clobazam was only used as polytherapy. Other polytherapies were not considered for further analysis as the numbers were small. However, monotherapy and polytherapy were compared and

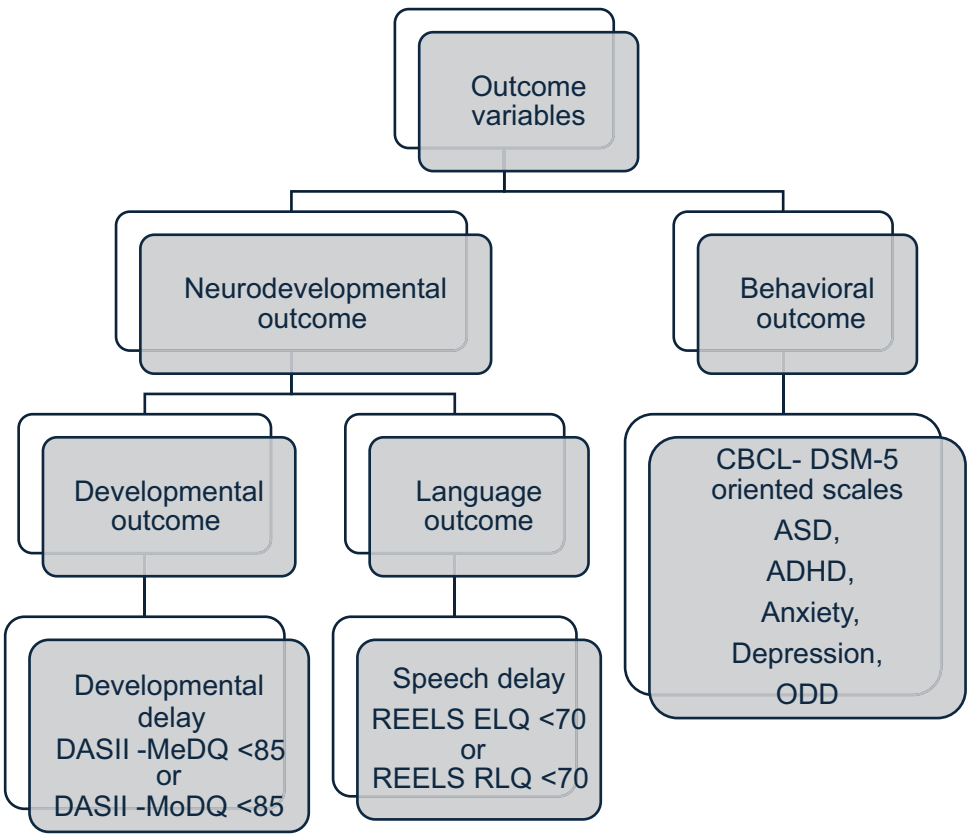


**Fig. 2** Outcomes variables. *ADHD* Attention deficit hyperactivity disorder, *ASD* Autism spectrum disorders, *CBCL* Checklist for behavior in children, *DASII* Developmental Assessment Scale for Indian Infants, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, fifth edition, *ELQ* Expressive language quotient, *MeDQ* Mental development quotient, *MoDQ* Motor development quotient, *ODD* Oppositional defiant disorder, *REELS* Receptive expressive emergent language scale, *RLQ* Receptive language quotient

**Table 2** Proportion of children who had impaired mental and motor development, and language functions in comparison to the control group

| | MeDQ < 85<br>*N* (%)<br>OR (95% CI) | MoDQ < 85<br>*N* (%)<br>OR (95% CI) | ELA REELS < 70<br>*N* (%)<br>OR (95% CI) | RLA REELS < 70<br>*N* (%)<br>OR (95% CI) |
|---|---|---|---|---|
| Controls (50) | 6 (12) | 4 (8) | 9 (18) | 6 (12) |
| Cases (97) | 10 (10.4)<br>0.85 (0.29, 2.50) | 2 (2.1)<br>0.25 (0.04, 1.39) | 34 (35.8)<br>2.54 (1.10, 5.85) | 21 (22.1)<br>2.08 (0.78, 5.56) |
| VPA Mono (14) | 3 (21.4)<br>2.00 (0.43, 9.29) | 0 (0)<br>— | 4 (28.6)<br>1.82 (0.47, 7.14) | 2 (14.3)<br>1.22 (0.22, 6.85) |
| CBZ Mono (20) | 1 (5)<br>0.39 (0.04, 3.43) | 1 (5)<br>0.61 (0.06, 5.78) | 6 (30)<br>1.95 (0.59, 6.47) | 4 (20)<br>1.83 (0.46, 7.35) |
| LEV Mono (10) | 0 (0) | 0 (0) | 2 (20)<br>1.14 (0.21, 6.29) | 0 |
| CLB Poly (21) | 3 (15)<br>1.29 (0.290, 5.769) | 0 (0) | 12 (60)<br>6.83 (2.17, 21.57) | 10 (50)<br>7.33 (2.158, 24.915) |

Odds ratio (with 95% confidence interval) is in comparison to the comparative group

*CLB* Clobazam, *CBZ* Carbamazepine, *ELA REELS* Expressive language age on REELS test, *LEV* Levetiracetam, *MeDQ* Mental development quotient, *MoDQ* Motor development quotient, *OR* Odds ratio, *RLA REELS* Receptive language age on REELS test, *VPA* Valproate

the differences in mean mental and motor quotient and RLQ and ELQ were assessed. It was seen that mean ELQ was statistically significantly higher for those in monotherapy compared to those in polytherapy (Table 3).

There was a weak negative correlation between clobazam dose in polytherapy and ELQ score (spearman correlation coefficient $r$ = -0.346, $p$ value = 0.125). There was a negligible negative correlation between RLQ score and clobazam dose (Spearman correlation coefficient $r$ = -0.09, $p$ value = 0.706).

The neurodevelopmental status was compared between KREP participants and comparative group (Table 3). The results showed that the mean RLQ of the participants and comparative group differed significantly with a $p$ value of 0.042. The mental and motor quotients of DASII did not differ significantly among the KREP participants and comparative group.

In the study group, Chi squared test was used to assess the association of Expressive Language Age (ELA) and Receptive Language Age (RLA) delay with possible confounders like gestational age, low birth weight, perinatal hypoxia and seizure during pregnancy. Among women with epilepsy who had children with normal ELQ, 14.3% (8/56) had seizures during pregnancy. Among women with epilepsy, who had children with ELA delay, 32.4% (11/34) had seizures during pregnancy. There was significant association between seizure during pregnancy and ELQ delay ($\chi 2 = 4.146$, $p$ value = 0.042)]. There was no association between ELA delay and the other variables.

Logistic regression was done among the study group to ascertain the effect of clobazam as polytherapy, gestational age and seizure in pregnancy based on the likelihood that children will have ELQ delay. The logistic regression model was statistically significant ($\chi 2 = 5.265$, $p$ value = 0.022). The model correctly classified 6.7% of the cases and explained 7.7% of the variance in the outcome variable. The final model only included clobazam as polytherapy as a significant predictor ($p$ value = 0.024). The odds ratio was 3.27.

In the study group, logistic regression was done to ascertain the effect of clobazam as polytherapy, gestational age and seizure in pregnancy based on the likelihood that children will have RLA delay. The logistic regression model was

**Table 3** Neurodevelopmental status comparison between participants receiving monotherapy and polytherapy; and comparison between KREP participants and comparative group

| | Monotherapy Mean (SD) | Polytherapy Mean (SD) | *T* | Sig (2 tailed) | KREP group Mean (SD) | Comparative group Mean (SD) | *T* | Sig (2 tailed) |
|---|---|---|---|---|---|---|---|---|
| ELA REELS | 88.14 (18.42) | 77.24 (18.72) | 2.59 | 0.01 | 90.1 (17.90) | 84.79 (19.09) | 1.62 | 0.11 |
| RLA REELS | 92.58 (16.39) | 86.56 (16.08) | 1.63 | 0.11 | 97.41 (12.42) | 90.73 (16.44) | 1.73 | 0.04 |
| MeDQ | 97.93 (10.75) | 94.49 (10.42) | 1.44 | 0.15 | 99.2 (10.07) | 96.84 (10.71) | 1.28 | 0.20 |
| MoDQ | 101.99 (9.26) | 101.28 (8.04) | 0.35 | 0.73 | 102.85 (10.62) | 101.76 (8.85) | 0.65 | 0.52 |

*ELA REELS* Expressive language age on REELS test, *KREP* Kerala Registry of Epilepsy and Pregnancy, *MeDQ* Mental development quotient, *MoDQ* Motor development quotient, *RLA REELS* Receptive language age on REELS test

statistically significant ($\chi 2 = 9.177$, $p$ value = 0.002). The model correctly classified 76.7% of the cases and explained 14.6% of the variance in the outcome variable. The final model only included clobazam as polytherapy as a significant predictor ($p$ value = 0.002). The odds ratio was 5.38.

Two children fulfilled the criteria for ASD in the DSM-5 scale of CBCL; one was a girl child, 26-mo-old; the mother was on LEV and clobazam during pregnancy. The second was a 30-mo-old boy; the mother was on topiramate during pregnancy. Only one child in the study group had sleep problems as per CBCL. None of the children fulfilled the criteria for anxiety or depression. There was no statistically significant difference in the behavioral outcomes between the study group and comparative group.

## Discussion

Most of the studies on cognitive and behavioral effects from *in utero* exposure to ASMs have shown a consistent association between VPA exposure and developmental delay measured, in most cases, with IQ test for older children and by tests such as the Bayley and DASII for younger children. In a study on polytherapy, the risk of major congenital malformations was 15.4% for CBZ plus VPA (OR 6.2; 95% CI 2.0–16.5) and 2.5% for CBZ plus any other ASM (OR 0.8; 95% CI 0.3–1.9) [17]. The same study also states that ASM polytherapy exposure probably reduces cognitive outcomes compared with ASM monotherapy. In a meta-analysis, VPA alone or combined with another ASM was found to be associated with the greatest odds of adverse neurodevelopmental outcomes compared with control [2]. Oxcarbazepine and LTG were associated with increased occurrence of autism. The finding of speech delay in children exposed to anti-seizure medications is significant because individuals with a history of childhood speech or language disorders may experience long-term difficulties in mental health, social well-being, and academic outcomes. In a review, it has been found that there is an association between childhood speech or language disorders and psychiatric disability, behavioral problems, lower socio-economic status, relationship and living difficulties, and lower academic achievement compared to the general population. It was seen that AED exposure, particularly in polytherapy or in higher cumulative dosages, is associated with lower developmental scores [18]. But in the present study, developmental scores did not differ according to the modality of AED exposure. Due to the non-availability of enough sample using these drugs, effect of sodium valproate and other drugs as monotherapy on neurodevelopmental outcomes could not be examined in this study.

There was no statistically significant difference in the behavioral outcomes between the study group and comparative group assessed using CBCL. A study examining behavioral functioning of children prenatally exposed to CBZ, LTG, LEV, or VPA monotherapy showed that prenatally exposed children showed an increased risk of behavioral problems [12]. Contrary to present study's finding, previous studies also show that use of LEV in people with epilepsy is associated with an increase in behavioral problems, including aggressive behavior [19, 20]. The lower age group of children selected for the study would also have affected the elicitation of behavior problems in the study group. In this study, two children had autism. Studies have shown that there is an increased risk of autism after prenatal VPA exposure, but not after prenatal LTG exposure [21, 22].

The major limitation of this paper is the relatively small population of participants. In the present study significant differences in outcome were not seen when the CBZ, LEV and sodium valproate were used as monotherapy. But when used as polytherapy with clobazam, statistically significant differences were seen in receptive and expressive language skills. Moreover, ELA was significantly reduced in children exposed to anti-seizure medications during pregnancy.

This study also underscores the necessity for structured monitoring of children exposed prenatally to ASM, aiming to strengthen preconception counselling and treatment choices for women of childbearing age.

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**Authors' Contributions** DB: Conceptualization, data collection and compilation of the article; ST: Academic support, coordinating the data collection and correction of the final document; LMS: Statistical analysis of the data. Dr. Babu George, Former Director, Child Development Centre, Medical College, Thiruvananthapuram will act as guarantor for this manuscript.

## Declarations

**Ethics Approval and Consent to Participate** The ethical approval for the study was obtained from the Institutional Ethics Committee of CDC. Written informed consent for participation was obtained from each parent.

**Consent for Publication** The institute consent form was given to the parent in vernacular language and the same was explained.

**Conflict of Interest** None.

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