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# Differential impact of antenatal exposure to antiseizure medications on motor and mental development in infants of women with epilepsy

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**ABSTRACT**

***Objective.*** We aimed to determine a possible association between motor and mental development in infants of women with epilepsy and antenatal exposure to antiseizure medication (ASM).

***Methods.*** Developmental paediatricians who were blinded to antenatal ASM exposure evaluated motor and mental development of infants (>12 months) using the Developmental Assessment Scale for Indian Infants (an Indian adaptation of the Bayley Scale of Infant Development). Motor (MODQ) and mental development quotients (MEDQ) were computed as ratios of respective developmental age to the chronological age of the child. We employed linear mixed models to study the relationship between antenatal exposure to ASM and the development quotients after adjustment for malformation status and age of the baby, maternal education and seizure type.

***Results.*** We studied 1,357 infants with mean age of 15.3±4.0 months (71.2% of all eligible infants). Infants were classified as having monotherapy or polytherapy, or unexposed in 840, 407 and 110 participants, respectively. The MEDQ of the polytherapy (92.9±14.9) and monotherapy (96.9±13.9) groups was lower than that of unexposed infants (99.8±12.5). Similarly, the MODQ of polytherapy (91.1 ±19.3) and monotherapy (96.6±17.5) groups was lower than that of unexposed infants (97.6±16.6). The differences in adjusted mean MEDQ were -7.4 (-11.4 to -4.3, $p$=0.001), -9.6 (-11.3 to -6.0, $p$=0.001) and -6.4 (-9.2 to -3.7, $p$=0.001) for valproate monotherapy, polytherapy with valproate and polytherapy without valproate, respectively. The adjusted mean MODQ also showed a similar trend. Those exposed to levetiracetam ($n$=62) had higher or similar adjusted MODQ (110.4 ±14.3; $p$=0.001) and MEDQ (104.3±9.1; $p$=0.09), compared to unexposed infants. A dose-dependent decrease in developmental indicators was observed for valproate and phenobarbitone.

***Significance.*** Antenatal exposure to ASM, especially valproate and phenobarbitone, adversely affects motor and mental development of exposed infants. Early developmental screening of high-risk infants is desirable.

**Key words:** epilepsy, pregnancy, antiepileptic drug, cognition, development

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Women constitute approximately half of the 50 million people with epilepsy globally [1]. Most women with epilepsy (WWE) require use antiseizure medication (ASM) in order to remain seizure-free during the pregnancy period. Women with childbearing potential and epilepsy have concerns about the risk of developmental impairment in infants with exposure to ASMs during pregnancy. Several prospective studies have demonstrated that antenatal exposure to ASMs can lead to impaired cognitive development at one-year [2], three-year [3], six-year [4-6] and ten-year follow-up time-points [7, 8]. Further, valproate (VPA) exposure carries the highest risk for language and intelligence deficits [4-6].

Prenatal and postnatal care, including good nutrition, protection against infections and psychological stimulation, are critical for development in infancy. Deficiencies in nutrition and psychological stimulation may jeopardise the physical, cognitive and emotional development of infants [9]. Some WWE face challenges in providing optimal care and support to their babies during the critical period of pregnancy and early infancy [10]. It is critical to identify children of WWE who are at risk of developmental problems in early infancy, as early detection of developmental delay provides opportunities to offer appropriate remedial therapies to the infants [11]. In this study, we aimed to assess the motor and mental developmental outcomes of infants of WWE according to antenatal exposure to ASM.

## Methods

### Study settings

The Kerala Registry of Epilepsy and Pregnancy (KREP) was started in 1998 as a prospective observational registry to monitor the maternal and foetal outcomes of pregnancies in WWE. The protocol of this registry has been published previously [2, 12, 13]. Briefly, KREP enrolled WWE in the pre-pregnancy stage or in the first trimester of pregnancy. All WWE were under the care of experienced epileptologists. Each pregnant woman in KREP maintained a pregnancy diary to record the daily use of ASMs, folic acid and seizure count. The data for each month of pregnancy and three postpartum months were transferred from the pregnancy diary to the clinical records of the registry during their clinic visits. Screening was carried out in four phases: screening for anomalies before 18 weeks of pregnancy, physical examination at birth, echocardiography, and abdomen ultrasonography at three months and physical review at 12 months. All infants were scheduled for evaluation at six years, 10-12 years and before 18 years.

### Study population

We included all babies in the registry who were over 12 months of age on 31$^{st}$ December, 2020. Infants older than 24 months of age were not included in this study. The demographic and clinical characteristics of the mothers were extracted from the medical records. Further, we reviewed the clinical charts and extracted the ASMs during pregnancy.

### Outcome measures

An independent team of developmental paediatricians and developmental therapists, who were blinded to the ASM exposure, had examined all infants after 12 months of age in their clinics. Infants who did not participate optimally were excluded from the study. The developmental assessment scale for Indian infants (DASII), which is an adaptation of the Bayley Scale of Infant Development Version I, was used for assessing motor and mental development [14]. The DASII is validated and widely used in India to assess infant development [15]. The DASII scale provided raw scores separately for motor and mental development based on a set of tests. The motor cluster included several test items for neck control (seven items), body control (23 items), locomotion I - coordinated movements (10 items), locomotion II - skills (13 items), and manipulations (14 items). Further, the mental cluster included test items for cognizance - visual (25 items), cognizance - auditory (seven items), manipulating and exploring (36 items), memory (11 items), social interaction and imitative behaviour (22 items), language- vocalization, speech and communication (11 items), language vocabulary and comprehension (18 items), understanding relationships (18 items), differentiating between use, shapes and movements (eight items) and manual dexterity (seven items). The motor and mental age of the child were computed separately by matching the respective raw scores with the standard score provided in the DASII manual. The motor development quotient (MODQ) and mental development quotient (MEDQ) were computed as the ratio of motor and mental age to chronological age. Infants of WWE who were not exposed to any ASM during pregnancy were classified as the internal comparison (reference) group. Infants exposed to ASM who had MODQ or MEDQ corresponding to less than one standard deviation of the mean MODQ or MEDQ of unexposed infants (reference group) were categorised with delayed development.

### Exposure

The main exposure variable of interest was the use of ASM anytime during the antenatal period. Infants were categorised into mono or polytherapy groups

based on number of ASMs used during pregnancy. The highest dose of each ASM used anytime during pregnancy was taken as the representative dosage of that ASM. Those infants with no exposure to ASM during the entire period of pregnancy were considered as the comparison group.

### Confounders

We extracted data of potential confounding variables regarding mother (age, seizure type, epilepsy classification) and baby (birth weight, malformation status) from the clinical records of the KREP.

### Statistical analysis

All data were transcribed to a spreadsheet (Microsoft Excel) and analysed using the Stata packages (STATA/MP 16.1). Continuous variables were summarized as mean with their standard deviations and discrete variables as proportions. Group comparisons were made with one-way ANOVA or chi square test, as appropriate. We employed linear mixed models to account for measured confounders while computing the adjusted motor and mental development quotients (aMODQ and aMEDQ). The deviations of the aMODQ and aMEDQ for each ASM group from the reference group (unexposed infants) were expressed as mean with 95% confidence interval.

We also examined the dose dependency of the development quotient (DQ) by comparing the DQ of infants with exposure to low, medium and high doses of ASMs. The dosage of ASMs were categorized as low, medium or high, as follows: carbamazepine (CBZ; low <400 mg, medium=401-800 mg, high >800 mg); lamotrigine (LTG; low <50 mg, medium=51-100 mg, high >100 mg); levetiracetam (LEV; low <500 mg, medium=501-1000 mg, high >1000 mg); oxcarbazepine (OXC; low <500 mg, medium=501-1000 mg, high >1000 mg); phenobarbitone (PB; low <45 mg, medium=46-60 mg, high >60 mg); phenytoin (PHT; low <100 mg, medium=101-200 mg, high >200 mg); and valproate (VPA; low<400 mg, medium=401-800 mg, high>800 mg). We employed similar linear mixed models to account for the effect of the measured confounding variables, as in our main model.

### Ethical oversight

The KREP is approved by the Institutional Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology (Approval No. SCTIEC/17/2003 dated 11 June 2003). Written informed consent was obtained from all WWE at the time of enrolment.

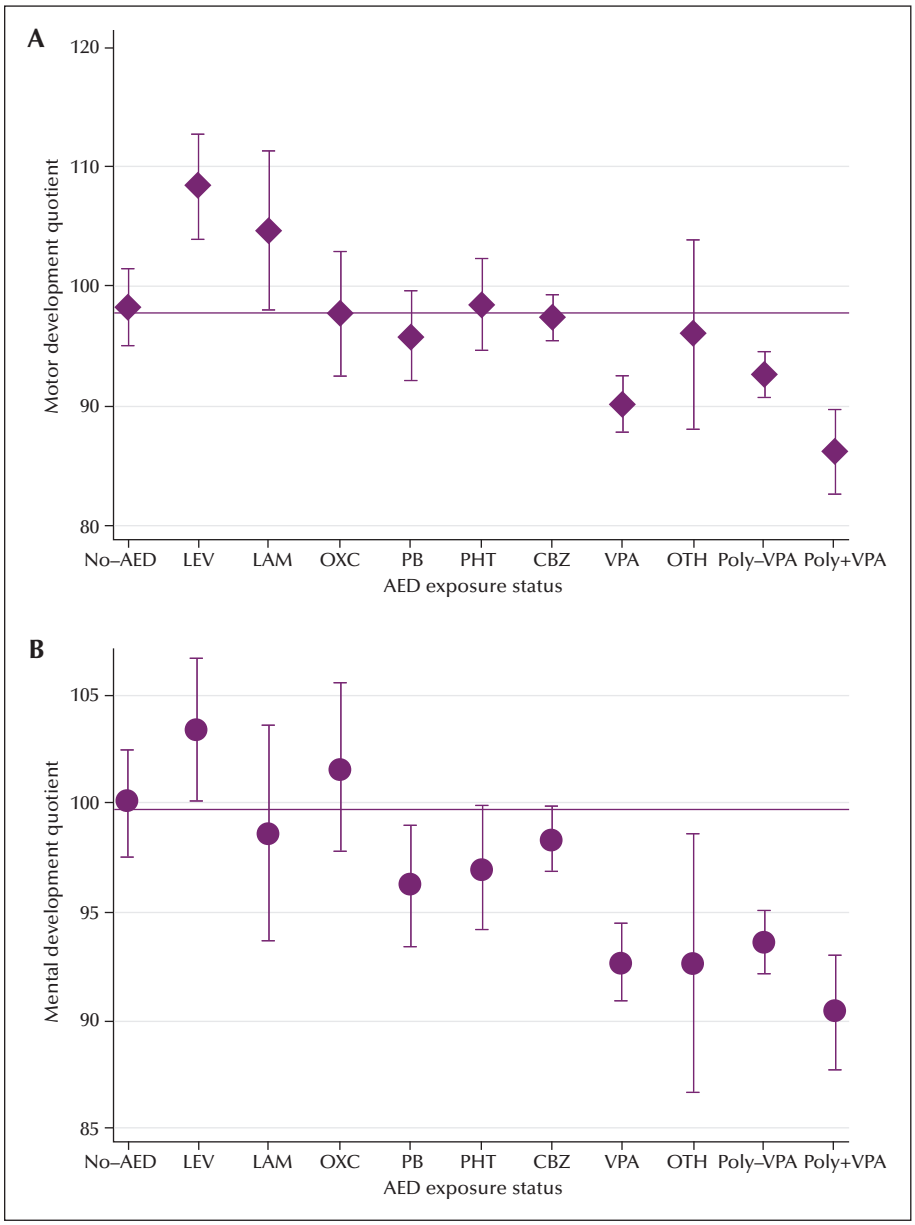
## Results

In total, 1,902 infants were eligible for this study (those who had completed the evaluation at three months and who were older than 12 months), of whom 1,485 (78.1%) were assessed. For other infants, the mothers declined, did not respond, could not keep their appointment, or could not be contacted. The developmental assessment was completed satisfactorily in 1,357 infants (71.2%). Tests were not completed for 128 infants, although these were included in the evaluation. There were 705 males and 652 females; 1,323 singleton pregnancies and 17 twin pregnancies. Their mean age (SD) was 15.3 (3.9) months. Congenital malformations were seen in 94 of the 1,357 infants included in the study. More than one third (37%) of WWE reported educational level corresponding to below the 10$^{th}$ grade (approximately 10 years of schooling). Their epilepsy was classified as generalized epilepsy in 39%. Generalised seizures were reported in 38% of WWE before the pregnancy period. The congenital malformation rate, age at examination of the infants and maternal education were comparable between those exposed to ASMs as monotherapy or polytherapy, or unexposed (*table 1*).

▼ **Table 1.** Characteristics of the study population according to ASM exposure.

| Variables | No-ASM (*n*=110) | Monotherapy (*n*=840) | Polytherapy (*n*=407) | *p* value# |
|---|---|---|---|---|
| Age in months, mean (SD) | 15.4 (3.8) | 15.3 (3.9) | 15.1 (4.0) | 0.759 |
| Birth weight in Kg, mean (SD) | 3.0 (0.5) | 2.9 (0.4) | 2.8 (0.5) | 0.030 |
| Malformations, *n* (%) | 7 (6.7) | 54 (6.4) | 33 (8.1) | 0.533 |
| Maternal education < 10 years, *n* (%) | 37 (33.9) | 310 (37.1) | 145 (35.9) | 0.774 |
| Generalised seizures, *n* (%) | 30 (27.3) | 360 (42.8) | 125 (30.7) | 00.001 |
| Generalised epilepsy, *n* (%) | 32 (29.1) | 373 (44.4) | 125 (30.7) | <0.001 |

#Statistical significance of continuous variables was estimated using the t test and proportions using the chi square test.




■ **Figure 1.** (A) Motor development quotient in infants according to ASM exposure. (B) Mental Development Quotient in infants according to ASM exposure.

The mean birth weight in the study population was 2.9 ±0.5 Kg. The birth weight of infants unexposed to ASMs (3.0±0.5 Kg) was significantly greater ($p$=0.03) than that of infants exposed to monotherapy (2.9 ±0.4 Kg), and those exposed to polytherapy (2.8 ±0.5 Kg,). The proportion of WWE who had generalized seizures during the index pregnancy was significantly higher ($p$<0.001) for the monotherapy group (360/840) than the polytherapy (125/407) and no ASM group (30/110) (*table 1*). None of the mothers reported smoking or alcohol habits during pregnancy.

Infants exposed to ASM *in utero* as monotherapy or polytherapy had lower MODQ and MEDQ than infants unexposed to ASM (*supplementary table 1*). The MODQ ranged from 88.9±13.4 in the clobazam monotherapy group to 110.4±14.3 in the LEV

▼ **Table 2.** Association between ASM exposure and motor development quotients.

| Variables | Unadjusted MODQ mean (SD) | Change in aMODQ; (95% CI)* | *p* value |
|---|---|---|---|
| No ASM, *n*=110 | 97.8 (16.6) | REF | |
| **ASM exposure as monotherapy** | | | |
| Carbamazepine, *n*=317 | 96.9 (16.4) | -0.8 (-4.6, 2.9) | 0.66 |
| Lamotrigine, *n*=26 | 106.3 (14.3) | 6.4 (-0.9, 13.8) | 0.08 |
| Levetiracetam, *n*=62 | 110.4 (14.3) | 10.1 (4.6, 15.6) | 0.001 |
| Oxcarbazepine, *n*=42 | 98.9 (16.5) | -0.5 (-6.6, 5.6) | 0.87 |
| Phenobarbitone, *n*=83 | 94.8 (18.5) | -2.4 (-7.4, 2.7) | 0.34 |
| Phenytoin, *n*=81 | 97.0 (17.2) | 0.3 (-4.7, 5.2) | 0.92 |
| Valproate, *n*=211 | 90.9 (17.9) | -8.1 (-12.2, -4.0) | 0.001 |
| All polytherapy, *n*=407 | 91.1 (19.3 ) | | |
| Polytherapy without VPA, *n*=315 | 92.6 (18.8) | -5.6 (-9.4, -1.9) | 0.003 |
| Polytherapy with VPA, *n*=92 | 86.2 (20.4) | -12.1 (-16.9, -7.2) | 0.001 |

*Adjusted for age of the baby, educational status of mother, malformations and seizure class.

monotherapy group (*supplementary table 2*). Similarly, the MEDQ ranged from 90.2+17.7 in the polytherapy group with VPA to 104.3±9.1 in the LEV monotherapy group. In the unexposed group, the mean MODQ and MEDQ were 97.7±16.6 and 99.8 ±12.5, respectively. In the polytherapy group, the corresponding mean MODQ and MEDQ were 91.1 ±19.3 and 92.9±14.9, respectively.

Infants exposed to ASM were classified in the delayed development group if their developmental quotients were less than one standard deviation of the mean MODQ (84) and MEDQ (88) of unexposed infants. Accordingly, the proportions of infants with delayed motor development for different ASM monotherapies were: LEV 1/62 (1.6%), LTG 1/26 (3.9%), OXC 6/42 (14.5%), PB 15/83 (18.1%), PHT 15/81 (18.5%), CBZ 58/317 (18.3%), VPA 69/211 (32.7%), other ASMs 2/18 (11.1%), polytherapy excluding VPA 92/315 (29.2%) and polytherapy including VPA 45/92 (48.9%). The proportions of infants with delayed mental development according to ASM exposure were: LEV 1/62 (1.6%), LTG 1/26 (11.5%), OXC 2/42 (4.7%), PB 21/83 (25.3%), PHT 21/80 (26.3%), CBZ 49/317 (15.5%), VPA 62/210 (29.5%), other ASMs 6/18 (33.3%), polytherapy without VPA 94/314 (29.9%) and polytherapy including VPA 34/92 (36.7%). Delay in motor and mental development was greater in the VPA monotherapy, VPA polytherapy and other polytherapy groups.

Infants exposed to VPA, compared to other ASMs, had significantly lower MODQ in the monotherapy (-8.1; 95% CI: -12.2 to -4.0) and polytherapy groups (-12.1; 95% CI: -16.9 to -7.2), after adjustment for maternal education, seizure classification, infant age at the time of examination and malformation status (*figure 1A, table 2*). In contrast, the mean adjusted MODQ was higher for the LEV monotherapy group (10.1; 95% CI: 4.6 to 15.6), compared to the unexposed group. The adjusted MEDQ of the VPA monotherapy group was lower than that of the unexposed group by -7.4 (95% CI: -10.4 to -4.3, *p*=<0.001) *(see figure 1B, table 3)*. The aMEDQ of the polytherapy group with VPA and without VPA was significantly (*p*<0.001) lower than that of unexposed infants (*see table 3, figure 1*). Further, those exposed to PB also showed lower adjusted mean MEDQ (-3.8; 95% CI: -7.5 to -0.1) than the unexposed group. These results remained consistent based on models adjusted for all the above-mentioned confounders and birth weight of infants (*supplementary table 3, 4*).

In the dose-response analysis, the dose dependent changes in aMODQ and aMEDQ were significant for VPA (aMODQ and aMEDQ), PB (aMODQ and aMEDQ) and CBZ (aMEDQ only). PB and LEV (aMEDQ only) showed a trend of lower aMODQ and aMEDQ with medium and high doses, compared to low dose of the same drug (*table 4*).

▼ **Table 3.** Association between ASM exposure and mental development quotients.

| Variables | Unadjusted MEDQ mean (SD) | Change in aMEDQ; (95% CI)* | *p* value |
|---|---|---|---|
| No ASM, *n*=110 | 99.8 (12.5) | REF | |
| **ASM exposure as monotherapy** | | | |
| Carbamazepine, *n*=317 | 98.4 (12.6) | -1.6 (-4.5, 1.2) | 0.25 |
| Lamotrigine, *n*=26 | 99.9 (10.3) | -1.3 (-6.8, 4.2) | 0.64 |
| Levetiracetam, *n*=62 | 104.3 (9.1) | 3.4 (-0.7, 7.5) | 0.1 |
| Others, *n*=18 | 91.8 (10.9) | -7.4 (-13.8, -0.9) | 0.02 |
| Oxcarbazepine, *n*=42 | 103.5 (11.0) | 1.7 (-2.9, 6.3) | 0.47 |
| Phenobarbitone, *n*=83 | 94.5 (14.9) | -3.8 (-7.5, -0.1) | 0.05 |
| Phenytoin, *n*=81 | 96.2 (14.2) | -2.9 (-6.6, 0.8) | 0.12 |
| Valproate, *n*=211 | 92.7 (15.4) | -7.4 (-10.4, -4.3) | 0.001 |
| All polytherapy *n*=407 | 92.9 (14.9) | | |
| Polytherapy without VPA, *n*=315 | 93.8 (13.9) | -6.4 (-9.2, -3.7) | <0.001 |
| Polytherapy with VPA, *n*=92 | 90.2 (17.7) | -9.6 (-13.2, -6.0) | <0.001 |

*Adjusted for age of the baby, educational status of the mother, malformations and seizure class

▼ **Table 4.** Dose response relationship between ASM and developmental indicators.

| | Motor development quotient* | | | Mental development quotient* | | |
|---|---|---|---|---|---|---|
| Drugs | Low dose | Medium dose | High dose | Low dose | Medium dose | High dose |
| Carbamazepine, *n*=534 | REF | -0.8 (-4.4, 2.7; *p*=0.64) | -4.4 (-8.7, -0.2); *p*=0.04 | REF | -0.8 (-4.4, 2.7; *p*=0.64) | -4.5 (-8.7, -0.2; *p*=0.04) |
| Lamotrigine, *n*=48 | REF | 6.7 (-8.7, 22.1; *p*=0.39) | 8.7 (-4.4, 21.7; *p*=0.19) | REF | -1.8 (-14.7, 11.0; *p*=0.78) | -0.1 (-11.0, 10.9; *p*=0.99) |
| Levetiracetam, *n*=113 | REF | -2.4 (-10.9, 6.2; *p*=0.59) | -7.7 (-15.9, 0.5; *p*=0.07 | REF | -1.1 (-6.3, 4.1; *p*=0.68) | -5.2 (=10.3, -0.1; *p*=0.04) |
| Oxcarbazepine, *n*=84 | REF | 1.4 (-12.8, 15.5; *p*=0.85) | -0.9 (-14.6, 12.7; *p*=0.89) | REF | 6.9 (-2.0, 15.8; *p*=0.12) | 5.6 (-2.9, 14.2; *p*=0.20) |
| Phenobarbitone, *n*=209 | REF | -3.5 (-11.7, 4.7; *p*=0.40) | -8.5 (-16.4, -0.7; *p*=0.03) | REF | -4.6 (-10.6, 1.5; *p*=0.14) | -7.2 (-12.9, -1.5; *p*=0.01) |
| Phenytoin, *n*=162 | REF | -0.6 (-10.5, 9.2); *p*=0.89 | | REF | -2.8 (-10.1, 4.4; *p*=0.44) | -5.3 (-12.4, 1.9; *p*=0.15) |
| Valproate, *n*=303 | REF | -8.9 (-13.2, -4.7; *p*=0.001) | -15.3 (-21.2, -9.5; *p*=0.001) | REF | | -11.4 (-16.3, -6.4; *p*=0.001) |

*Adjusted for age of the baby, educational status of mother, malformations and seizure class.
Levetiracetam (low<500 mg, medium=501-1000 mg, high>1000 mg); lamotrigine (low<50 mg, medium=51-100 mg, high>100 mg); oxcarbazepine (low<500 mg, medium=501-1000 mg, high>1000 mg); phenobarbitone (low<45 mg, medium=46-60 mg, high>60 mg); phenytoin (low<100 mg, medium=101-200 mg, high>200 mg); carbamazepine (low<400 mg, medium=401-800 mg, high>800 mg); valproate (low<400 mg, medium=401-800 mg, high>800 mg).

## Discussion

The KREP is a prospective register that aims to capture the developmental trajectories of children of WWE from early infancy to late adolescence. This evaluation of children in the registry at one year is the first of four assessments up to 18 years. The instrument that we used had a fair distribution of tests, aimed at assessing receptive and expressive language development as well as other cognitive functions, although it was a generic test.

We demonstrated that motor and mental development of infants of WWE varied widely according to antenatal ASM exposure. Within the monotherapy subgroups, VPA stood out with the lowest developmental quotients followed by PB and PHT. Polytherapy that included VPA as well as polytherapy without VPA was associated with significant developmental delay. Further, the dose-dependent decrease in development quotients with exposure to both VPA and phenobarbitone that was observed in this study indicates a causal relationship between the two factors. In contrast, infants exposed to LEV and LTG did not show any developmental impairment. There are very few prospective studies that have examined developmental outcome at one year for infants exposed to ASM. A prospective study of two-year-old children did not show a significant difference in motor and mental (cognitive) development between children of healthy women and children of WWE with antenatal exposure to LEV or LTG [16]. The present study demonstrates that ASMs differ widely regarding adverse developmental effects; viz VPA and PB showed the greatest adverse effect, while most other ASMs showed minimal to mild adverse effects. According to an earlier study, prenatal exposure to PHT is associated with lower mental development scores in infants at one year [17]. However, other studies on exposure to CBZ have yielded variable results ranging from normal intelligence [18] to low intelligence quotients [19,20]. The negative impact of VPA exposure on neurocognitive development is well established in older children [3-6, 18, 21, 22].

The dose response relationship for VPA further strengthens the causal association between intrauterine exposure and developmental outcomes. It is debatable whether exposure to a single ASM at high dose is more harmful than two drugs at low doses in terms of developmental outcome. In this cohort, polytherapy including and excluding VPA was associated with a substantial risk of developmental developmental impairment. A network meta-analysis also demonstrated significant impairment of intelligence, psychomotor development and behavioural problems with polytherapy including and excluding VPA [23]. More observational data are required to support the hypothesis of the effectiveness of two ASMs at low dose for the management of seizures in women of reproductive age.

The precise mechanisms that mediate the developmental adverse effects of ASMs have been investigated. In a population-based study from Sweden, newborns exposed to VPA and CBZ *in utero* had a smaller head circumference [24]. Reduced grey matter volume and abnormal network connectivity for language nodes were also reported in children exposed to ASMs *in utero* [25, 26]. Further, voxel-based morphometric magnetic resonance imaging (MRI) showed focal thinning of the cerebral cortex over language areas in exposed children [27]. Neuronal apoptosis is an important pathway for ASM-induced brain changes that eventually lead to neurocognitive deficits. In animal experimental studies, mice that were exposed to VPA, PB or PHT *in utero* showed a relatively higher level of neuronal apoptosis [28], whereas those exposed to LEV, LTG and CBZ did not show similar changes [29].

The strength of our study is the large prospective cohort of children with well characterized antenatal ASM exposure status and detailed documentation of early developmental outcome measures. In our study, we were able to compare between exposure to newer ASMs, older ASMs and no exposure to any ASMs. The developmental outcomes determined at one year, however, may not be entirely representative of delays in several domains, especially language-related developmental delays. Although the tool used for assessment was validated in Indian settings, the scores generated from this tool for different domains may not be directly comparable to scores generated from other international tools. Non-availability of ASM plasma concentration in pregnancy is an important limitation in interpreting observations related to dose response.

## Conclusion

Our study strengthens the hypothesis that the negative impact of antenatal exposure to ASM is specific to certain ASMs, such as VPA and PB. Newer ASMs, such as LEV and LTG, are relatively safer in preventing developmental impairments in children. It is important for children of WWE exposed to VPA, PB and polytherapy to be examined at 12 months in order to detect any developmental delay, as the negative developmental impact of such exposure can be detected as early as 12 months. Our findings offer an opportunity to make pregnancies safer by avoiding the use of VPA and other high-risk ASMs in women of childbearing potential. ■

## Key points

- Exposure to valproate, phenobarbitone and polytherapy of antiseizure medications during pregnancy is associated with a relatively high risk of developmental delay.
- Infants exposed to lamotrigine or levetiracetam *in utero* did not show developmental impairment.
- Developmental quotients showed a dose-dependent association with valproate and phenobarbitone with a similar trend for other antiseizure medications.

**Supplementary material.**
Supplementary tables and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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## References

1. World Health Organization. *Epilepsy*. WHO. 2019. https://www.who.int/news-room/fact-sheets/detail/epilepsy

2. Thomas SV, Ajaykumar B, Sindhu K, Nair MK, George B, Sarma PS. Motor and mental development of infants exposed to antiepileptic drugs *in utero*. *Epilepsy Behav* 2008; 13(1): 229-36.

3. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, *et al*. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009; 360(16): 1597-605.

4. Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. *Epilepsia* 2007; 48(12): 2234-40.

5. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, *et al*. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; 12(3): 244-52.

6. Bromley RL, Mawer GE, Briggs M, Cheyne C, Clayton-Smith J, García-Fiñana M, *et al*. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 2013; 84 (6): 637-43.

7. Unnikrishnan G, Jacob NS, Salim S, Jose M, Salini RA, Pavithran V, *et al*. Enduring language deficits in children of women with epilepsy and the potential role of intrauterine exposure to antiepileptic drugs. *Epilepsia* 2020; 61(11): 2442-51.

8. Gopinath N, Muneer AK, Unnikrishnan S, Varma RP, Thomas SV. Children (10-12 years age) of women with epilepsy have lower intelligence, attention and memory: observations from a prospective cohort case control study. *Epilepsy Res* 2015; 117: 58-62.

9. Lake A. Early childhood development - global action is overdue. *Lancet* 2011; 378(9799): 1277-8.

10. Saramma PP, Thomas SV, Sarma PS. Child rearing issues for mothers with epilepsy: a case control study. *Ann Indian Acad Neurol* 2006; 9(3): 158.

11. CDC. *Why act early if you're concerned about development?* Centers for Disease Control and Prevention. 2021. https://www.cdc.gov/ncbddd/actearly/whyActEarly.html

12. Thomas SV, Indrani L, Devi GC, Jacob S, Beegum J, Jacob PP, *et al*. Pregnancy in women with epilepsy: preliminary results of Kerala registry of epilepsy and pregnancy. *Neurol India* 2001; 49(1): 60-6.

13. Thomas SV, Jose M, Divakaran S, Sankara Sarma P. Malformation risk of antiepileptic drug exposure during pregnancy in women with epilepsy: results from a pregnancy registry in South India. *Epilepsia* 2017; 58(2): 274-81.

14. Phatak P. *Mental and motor growth of Indian babies (1 month-30 months). (Longitudinal growth of Indian children)*. Final Report. 1970.

15. Nair MKC, Krishnan R, Harikumaran Nair GS, Bhaskaran D, Leena ML, George B, *et al*. CDC Kerala 4: TDSC items based developmental therapy package among low birth weight babies - outcome at 18 months using DASII. *Indian J Pediatr* 2014; 81(Suppl 2): S85-90.

16. Meador KJ, Cohen MJ, Loring DW, May RC, Brown C, Robalino CP, *et al*. Two-year-old cognitive outcomes in children of pregnant women with epilepsy in the maternal

outcomes and neurodevelopmental effects of antiepileptic drugs study. *JAMA Neurol* 2021; 78(8): 927-36.

17. Scolnik D, Nulman I, Rovet J, Gladstone D, Czuchta D, Gardner HA, *et al*. Neurodevelopment of children exposed *in utero* to phenytoin and carbamazepine monotherapy. *JAMA* 1994; 271(10): 767-70.

18. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, *et al*. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004; 62(1): 28-32.

19. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; 75(6): 517-20.

20. Matlow J, Koren G. Is carbamazepine safe to take during pregnancy? *Can Fam Physician* 2012; 58(2): 163-4.

21. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. *Drug Saf* 2010; 33(1): 73-9.

22. Blotière PO, Miranda S, Weill A, Mikaeloff Y, Peyre H, Ramus F, *et al*. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. *BMJ Open* 2020; 10(6): e034829.

23. Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, *et al*. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open* 2017; 7(7): e017248.

24. Almgren M, Källén B, Lavebratt C. Population-based study of antiepileptic drug exposure *in utero* - influence on head circumference in newborns. *Seizure* 2009; 18(10): 672-5.

25. Sreedharan RM, Sheelakumari R, Anila KM, Kesavadas C, Thomas SV. Reduced brain volumes in children of women with epilepsy: a neuropsychological and voxel based morphometric analysis in pre-adolescent children. *J Neuroradiol* 2018; 45(6): 380-5.

26. Sreedharan RM, Kesavadas C, Aiyappan S, Anila KM, Mohan AC, Thomas SV. Functional language network connectivity in children of women with epilepsy with selective antenatal antiepileptic drug exposure. *Ann Indian Acad Neurol* 2020; 23(2): 167.

27. Wood AG, Chen J, Barton S, Nadebaum C, Anderson VA, Catroppa C, *et al*. Altered cortical thickness following prenatal sodium valproate exposure. *Ann Clin Transl Neurol* 2014; 1(7): 497-501.

28. Manthou ME, Meditskou S, Lykartsis C, Sapalidis K, Sorkou K, Emmanouil-Nikoloussi E-N. The role of neuronal apoptosis in Valproic Acid brain-related teratogenesis: a histochemical and immunohistochemical study in BALB/c mice. *Rom J Morphol Embryol* 2020; 61(3): 813-9.

29. Kaushal S, Tamer Z, Opoku F, Forcelli PA. Anticonvulsant drug induced cell death in the developing white matter of the rodent brain. *Epilepsia* 2016; 57(5): 727-34.

## TEST YOURSELF

**(1) Is the motor and mental development of infants from pregnancies of women with epilepsy exposed to ASM *in utero* inferior to that of unexposed infants?**

**(2) Which ASMs may impact infant development?**

**(3) What is the developmental outcome of infants exposed to newer ASMs, such as lamotrigine or levetiracetam?**

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*