



Antiseizure medication use in pregnancy and the risk of poor fetal growth in the EURAP international registry: a prospective cohort study

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Summary

Background Poor fetal growth is a major cause of perinatal morbidity and mortality and predisposes individuals to chronic diseases in adulthood. Antiseizure medication use in pregnancy has been linked with poor fetal growth, but this association has received little attention and its multifaceted aspects remain unclear. We investigated the risk of poor fetal growth in infants exposed prenatally to antiseizure monotherapy versus polytherapy, across different antiseizure monotherapies, and across common antiseizure medication combinations.

Methods This prospective, observational, longitudinal cohort study was based on singleton livebirths of women (aged 14–55 years at conception) with epilepsy on antiseizure medication and enrolled at any point in pregnancy into the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) between June 20, 1999, and Nov 15, 2023. Follow-up data were acquired after each trimester and at delivery. Multivariable models were used to assess the association of antiseizure medication exposures with different fetal growth indicators: birthweight centile (primary outcome); small for gestational age (SGA; birthweight <10th centile for gestational age); severe SGA (birthweight <3rd centile); and low birthweight (<2500 g). Models were adjusted for a wide range of clinical and demographic factors that could influence the association between antiseizure medication exposure and poor fetal growth.

Findings The primary outcome analysis included 15 893 offspring prenatally exposed to antiseizure medications (12 911 exposed to monotherapy and 2982 to polytherapy). The other analyses were limited to one offspring per mother and included 13 728 offspring (11 142 exposed to monotherapy and 2586 to polytherapy). Compared with offspring exposed to monotherapy, those exposed to polytherapy had a lower birthweight centile (adjusted unstandardised model coefficient [*b*] −2.74 [95% CI −4.22 to −1.26]) and an approximately 50% higher risk of SGA (adjusted odds ratio [OR] 1.48 [95% CI 1.29 to 1.70]), severe SGA (1.49 [1.22 to 1.83]), and low birthweight (1.50 [1.15 to 1.95]). Birthweight centile decreased with increasing number of concomitant antiseizure medications (adjusted *b* −14.18 [95% CI −24.07 to −4.29] with four antiseizure medications [*n*=48] relative to monotherapy). Among monotherapies, birthweight centile was lower (in decreasing order) with topiramate (adjusted *b* −11.93 [95% CI −16.72 to −7.15], *n*=248), phenobarbital (−8.08 [−11.89 to −4.26], *n*=431), oxcarbazepine (−5.10 [−8.24 to −1.96], *n*=557), carbamazepine (−3.15 [−5.01 to −1.28], *n*=2797), valproic acid (−2.54 [−4.50 to −0.58], *n*=1829), and levetiracetam (−2.51 [−4.38 to −0.63], *n*=1809) compared with lamotrigine (*n*=4672). Offspring exposed to carbamazepine and levetiracetam in combination (*n*=173) had a lower birthweight centile (adjusted *b* −6.27 [95% CI −12.03 to −0.50]) than those exposed to lamotrigine monotherapy. No differences in birthweight centile were found between offspring exposed to lamotrigine monotherapy and those exposed to lamotrigine in combination with either levetiracetam (adjusted *b* 0.19 [95% CI −2.67 to 3.06], *n*=470) or valproic acid (0.11 [−3.59 to 3.82], *n*=258).

Interpretation In addition to congenital malformations and neurodevelopmental effects, poor fetal growth should be regarded as an important adverse outcome of prenatal antiseizure medication exposure. Risk varies across individual antiseizure monotherapies and specific antiseizure combinations and increases with the number of concomitant antiseizure medications. These findings have important implications for preconception counselling and management, including risk prediction and individualised treatment selection.

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Introduction

Antiseizure medications are among the top ten classes of medicines (excluding vitamins) used during the first trimester of pregnancy.¹ Although antiseizure

medications are usually continued throughout pregnancy to minimise serious harm resulting from worsening of the underlying condition, exposure to these drugs entail risks for the developing fetus. Historically, attention has

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Research in context

Evidence before this study

Research into the risks associated with prenatal exposure to antiseizure medications has focused largely on major congenital malformations and postnatal neurodevelopmental disorders. In 2025, we published a systematic review and meta-analysis of studies on the risk of other adverse pregnancy outcomes after prenatal antiseizure medication exposure. Applying the same methodology, we searched EMBASE, MEDLINE, Cochrane, and OVID for articles published in English from Aug 2, 2023 (last date covered by our initial search), to Oct 15, 2025, using the search terms “pregnan*” combined with “antiepilep*”, “anticonvuls*” or “antiseizure”, “acetazolamide”, “brivaracetam”, “cannabidiol”, “carbamazepine”, “cenobamate”, “clobazam”, “clonazepam”, “diazepam”, “eslicarbazepine”, “ethosuximide”, “felbamate”, “gabapentin”, “ganaxolone”, “lacosamide”, “lamotrigine”, “levetiracetam”, “nitrazepam”, “oxcarbazepine”, “perampanel”, “phenobarbit*”, “phenytoin”, “piracetam”, “pregabalin”, “primidone”, “retigabine”, “rufinamide”, “stiripentol”, “sulthiame”, “tiagabine”, “topiramate”, “valpro*”, “vigabatrin”, “zonisamide”, “pregnan* outcome”, “adverse pregnan* outcome”, “birthweight”, “intrauterine growth”, “fetal growth”, or “small for gestational age”. All studies retrieved were observational by necessity, and most had major methodological shortcomings such as a retrospective design or a sample size insufficient to adequately control for confounders. Overall, available data suggest that prenatal exposure to antiseizure medications is associated with an increased risk of poor fetal growth, but evidence is inconclusive, mainly due to the possibility of confounding by indication. Data are also scarce and conflicting on the comparative risk associated with polytherapy and with individual antiseizure monotherapies, and the possibility of the risk being dose dependent.

Added value of this study

This prospective cohort study provides, to our knowledge, the largest prospective dataset on fetal growth outcomes in offspring exposed prenatally to antiseizure medications. Because of the large sample size and ability to adjust for numerous confounders, this study made it possible for the first time to establish comparative risks of poor fetal growth not only after exposure to antiseizure polytherapy and monotherapy assessed as a whole, but also to individual antiseizure medications, different types of antiseizure combinations, number of seizures in pregnancy, and other relevant variables.

Implications of all the available evidence

Poor fetal growth is a major cause of perinatal morbidity and mortality, with lasting complications extending into adult life. Available evidence now indicates that prenatal exposure to antiseizure medications is significantly associated with an increased risk of poor fetal growth. For women with active epilepsy, withholding antiseizure therapy is not generally an option, and the key clinical question is not whether treatment can be avoided, but what treatment is safest. Therefore, knowledge that the risk of poor fetal growth increases with increasing number of concomitantly taken antiseizure medications and varies across monotherapies and antiseizure medication combinations has important implications for optimisation of antiseizure therapy preconception. Together with the risk of major congenital malformations and postnatal neurodevelopmental disorders, the risk of poor fetal growth associated with prenatal antiseizure medication exposure and other clinical and demographic factors should be taken into consideration in the management of women of childbearing potential and should be part of preconception counselling.

focused on the risk of major congenital malformations and postnatal neurodevelopmental disorders. Poor fetal growth—another adverse outcome reportedly associated with prenatal antiseizure medication exposure²—is mentioned as a concern in practice guidelines^{3,4} but has received considerably less attention. However, poor fetal growth has major public health implications: it is an important cause of perinatal morbidity and mortality⁵ and has lasting complications, including developmental delay,⁶ reduced academic or professional attainment,⁷ and greater likelihood of developing depression⁸ and chronic diseases (eg, diabetes, impaired respiratory function, and cardiovascular disease) later in life.⁹

Poor fetal growth after prenatal antiseizure medication exposure is underemphasised compared with other adverse outcomes for several reasons. Fewer studies have addressed this topic, with most having methodological shortcomings, such as a retrospective design^{10–17} or a sample size insufficient to adequately control for confounders.^{12,16} Establishing a causative link between

prenatal antiseizure medication exposure and poor fetal growth has also been challenging, owing to possible confounding by indication¹⁰ and inadequate characterisation of the role of other variables, such as the occurrence of seizures during pregnancy.^{18–20} Even systematic reviews and meta-analyses in the past 3 years have failed to shed light on this issue. An increased risk of poor fetal growth in antiseizure medication-exposed pregnancies compared with unexposed pregnancies with the same indication was identified by two meta-analyses,^{2,21} but not by the most recent study,²² which ascribed their discrepant results to methodological differences across studies. A causative link between prenatal antiseizure medication exposure and poor fetal growth is suggested by reports that the risk might be greater among offspring exposed to polytherapy compared with monotherapy^{19,22} and might vary by antiseizure medication type.^{11–15,19} However, evidence on the comparative risk associated with individual antiseizure medications is inconclusive, and little

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See Online for appendix

information is available regarding dose dependency. Addressing these knowledge gaps is imperative for evidence-based preconception counselling, and for informed decisions to reduce the risk of poor fetal growth and its short-term and long-term complications.

We comprehensively investigated the multifaceted association between prenatal antiseizure medication exposure and poor fetal growth through a prospective study across 47 countries and five continents. We assessed the risk of poor fetal growth, as measured by different indicators: between antiseizure medication monotherapy and polytherapy; across different antiseizure medication monotherapies and their doses; and in relation to the most common antiseizure medication combinations. We also evaluated the role of a range of factors that potentially influence the association between prenatal antiseizure medication exposure and risk of poor fetal growth.

Methods

Study design and participants

Data were collected as part of the International Registry of Antiepileptic Drugs and Pregnancy (EURAP), a prospective, observational, longitudinal cohort study established in 1999 to assess pregnancy outcomes after antiseizure medication exposure, comprising a network of more than 1500 physicians from 47 countries. The protocol, which has been described previously,^{23,24} received ethics approval from all participating centres. All participants provided written, informed consent before enrolment. The present analysis included singleton pregnancies in women (aged 14–55 years at conception) with epilepsy exposed to antiseizure medications from conception to delivery and enrolled between June 20, 1999, and Nov 15, 2023. Data were extracted on March 26, 2024. We used the following criteria to exclude pregnancies from the current analysis: those in women without epilepsy (0.7% of the cohort); those during which the fetus was exposed to other teratogens or comorbidities (eg, diabetes) known to be associated with altered fetal development; those during which antiseizure medications were added or discontinued; those without follow-up until delivery or enrolment after delivery; those that did not lead to delivery or when there was insufficient information to determine fetal outcome (ie, whether a major congenital malformation was present or not); and those resulting in stillbirth or offspring with major congenital malformations or genetic or chromosomal abnormalities. We followed the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guidelines.

Procedures

Sex and ethnicity data were established by the reporting physician through interview with the mother and medical record review. Reporting physicians provided demographic and health information on offspring and mothers, including maternal epilepsy classification (categorised as

focal, generalised, and undetermined), occurrence of seizures during pregnancy (categorised as tonic-clonic, including generalised tonic-clonic and focal-to-bilateral tonic-clonic; and other seizure types), antiseizure medication exposures, parental history of major congenital malformations (excluding cerebral malformations causally linked to maternal epilepsy), maternal folate intake (categorised as preconception and after conception, after conception only, and no intake or underdosed),²⁵ and other risk factors of poor fetal growth. Follow-up data were acquired after each trimester and at delivery.

Outcomes

The primary aim was to determine whether the risk of poor fetal growth differs between antiseizure medication monotherapy and polytherapy exposure, and whether this risk is influenced by the number of antiseizure medications taken during pregnancy. As secondary aims, we assessed the association of poor fetal growth with exposure to individual antiseizure medications, its dose-dependency, and associations with various demographic and clinical variables, selected *a priori* based on review of the literature (appendix p 11). In a post-hoc analysis, we also explored the risk of poor fetal growth among the most common polytherapies.

Birthweight centile (Hadlock based,^{26,27} corrected for gestational age) as a continuous variable was selected as the primary outcome because of evidence that the risk of adverse outcomes—such as perinatal mortality, poor condition at birth (Apgar <7 at 5 min), and reduced cognitive and educational performance in childhood—is not confined to infants who are small for gestational age (SGA) but increases as birthweight centile falls, even for infants with weight appropriate for gestational age (≥ 10 th centile).^{28–31} As secondary outcomes, we determined three categorical measures of poor fetal growth—that is, SGA (defined as birthweight <10th centile for gestational age), severe SGA (defined as birthweight <3rd centile for gestational age), and low birthweight (defined as birthweight <2500 g).

Statistical analysis

Separate linear models were used to investigate the relationship between each fetal growth indicator and antiseizure medication exposure. Generalised linear mixed models were used to model birthweight centile. Logistic regression models were used for SGA, severe SGA, and low birthweight. All models were adjusted for: calendar year of pregnancy (included as a linear term), offspring sex, geographical region, maternal age, parental history of major congenital malformations, maternal epilepsy type, occurrence of tonic-clonic seizures during pregnancy, occurrence of other seizure types during pregnancy, primigravida status, tobacco smoking during pregnancy, alcohol consumption during pregnancy, and folate intake. We adjusted for seizures because previous reports have linked their occurrence

during pregnancy with poor fetal growth.^{18–20} No adjustment was made for maternal ethnicity because its inclusion in the models introduced significant collinearity (variance inflation factor >10), mainly due to its strong association with region of enrolment. Models for low birthweight were also adjusted for gestational age. When appropriate, random intercepts for the mother were specified to account for those who had two or more offspring. Owing to failure of model convergence, only one offspring per mother (the first recorded in EURAP in the case of multiple offspring) was included in the logistic regression models. Models were initially estimated in offspring exposed to any antiseizure medication, assessing first the effect of monotherapy versus polytherapy, and then that of number of antiseizure medications (one through to four or more, using monotherapy as reference). In sensitivity analyses, the effect of monotherapy versus polytherapy was further investigated in four separate models: (1) with additional adjustment for maternal and paternal educational levels (categorised as low and medium or high),²³ available for all regions of enrolment except for Australia and New Zealand; (2) with greater stratification of maternal folate intake (preconception and after conception; after conception only; underdosed; and no intake); (3) with additional adjustment for total number of seizures (categorised as no seizures during pregnancy; 1–9 seizures; and ≥ 10 seizures); and (4) limited to offspring born to mothers who were seizure-free during pregnancy (in this analysis, occurrence of tonic-clonic seizures or other seizure types during pregnancy were dropped from the model owing to inherent redundancy).

Models were subsequently applied to offspring exposed to antiseizure medication monotherapy only, with the specific monotherapy entered as a predictor. Lamotrigine was used as reference because it is generally regarded as the safest antiseizure medication with respect to fetal outcomes^{2,19,22} and was also the most common exposure. The association of dose with each fetal growth indicator was investigated by modelling maternal daily doses at conception, expressed as prescribed daily dose divided by defined daily dose separately for each antiseizure medication, where the defined daily dose is the average maintenance dose per day for a drug used for its primary indication in adults as defined by WHO. When there was evidence of a dose–response relationship for any categorical outcome, a computational approach²³ was used to determine dose ranges associated with increased risk for that outcome. Briefly, this method objectively assesses all plausible splits of dose ranges.²³ A logistic regression model was then used to compare outcome risk across dose ranges, adjusting for the same variables listed above.

In view of the results on offspring exposed to antiseizure medication monotherapy, we also explored

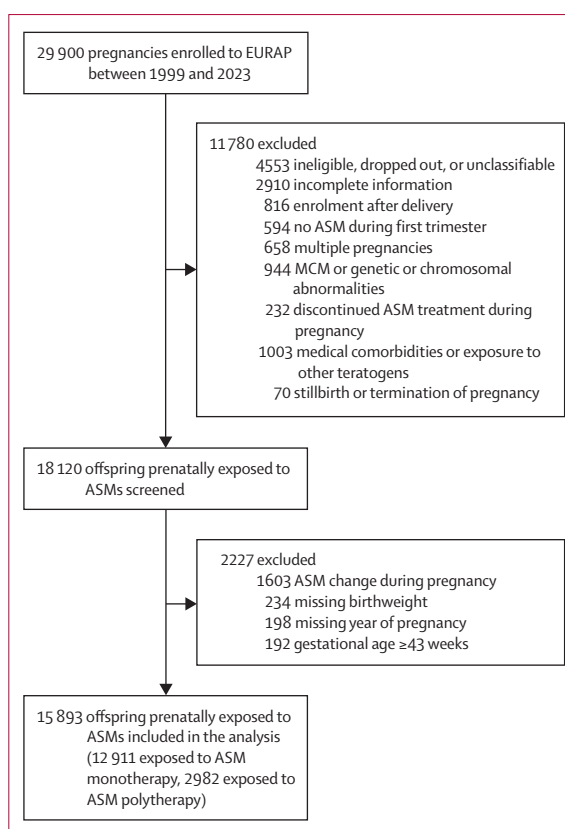


Figure 1: Study profile

ASM change during pregnancy refers to participants who started or discontinued one or more ASMs during pregnancy. ASM=antiseizure medication. MCM=major congenital malformation.

the association between each fetal growth indicator and different antiseizure medication exposure subsets. We first re-ran models for monotherapy versus polytherapy among offspring exposed only to carbamazepine, lamotrigine, levetiracetam, phenytoin, or valproic acid (either alone or in combination with each other). We then applied models to offspring exposed to either the most common polytherapies (each with ≥ 150 exposed offspring) or lamotrigine monotherapy, with the specific exposure entered as a predictor and lamotrigine used as the reference.

For all analyses, parameters are presented as either unstandardised model coefficients (*b*) or exponentiated model coefficients (odds ratios [ORs]) with 95% CIs. The widths of the intervals were adjusted for family-wise multiplicity using the Benjamini–Hochberg procedure to control the false discovery rate at $q=5\%$. Based on the empirical heuristic that the total sample should be greater than ten times the number of predictor variables, the sample size (>10 000) was deemed to be appropriate. Missing data were not assumed to be missing at random, so separate levels were added to categorical variables to estimate the effect of missing data in all models.

	Overall (n=15 893)	Antiseizure monotherapy (n=12 911)	Antiseizure polytherapy (n=2982)
Offspring characteristics			
Sex			
Female	7672 (48.3%)	6286 (48.7%)	1386 (46.5%)
Male	8209 (51.6%)	6615 (51.2%)	1594 (53.4%)
Unknown	12 (0.1%)	10 (0.1%)	2 (0.1%)
Year of birth			
1999–2003	2197 (13.8%)	1793 (13.9%)	404 (13.5%)
2004–08	4414 (27.8%)	3655 (28.3%)	759 (25.5%)
2009–13	4044 (25.4%)	3334 (25.8%)	710 (23.8%)
2014–18	3268 (20.6%)	2634 (20.4%)	634 (21.3%)
2019–23	1970 (12.4%)	1495 (11.6%)	475 (15.9%)
Gestational age at birth, weeks	39.5 (1.8)	39.6 (1.8)	39.4 (2.0)
Birthweight, g	3313.9 (554.7)	3335.3 (547.4)	3226.0 (584.4)
Birthweight centile	37.4 (28.4)	38.2 (28.4)	34.1 (28.5)
Birthweight categories			
SGA (<10th centile)	3233 (20.3%)	2446 (18.9%)	787 (26.4%)
Severe SGA (<3rd centile)	1207 (7.6%)	878 (6.8%)	329 (11.0%)
Low birthweight (<2500 g)	971 (6.1%)	692 (5.4%)	279 (9.4%)
Mothers' characteristics			
Maternal age at conception, years	30.0 (5.0)	30.0 (4.9)	29.9 (5.1)
Maternal ethnicity			
White	13 569 (85.4%)	11 170 (86.5%)	2399 (80.4%)
African	36 (0.2%)	28 (0.2%)	8 (0.3%)
Asian	1719 (10.8%)	1268 (9.8%)	451 (15.1%)
Mixed	262 (1.6%)	183 (1.4%)	79 (2.6%)
North African	92 (0.6%)	70 (0.5%)	22 (0.7%)
Other	189 (1.2%)	169 (1.3%)	20 (0.7%)
Unknown	26 (0.2%)	23 (0.2%)	3 (0.1%)
Region of enrolment			
Western Europe	3962 (24.9%)	3300 (25.6%)	662 (22.1%)
Australia and New Zealand	1192 (7.5%)	903 (7.0%)	289 (9.7%)
Eastern Europe	863 (5.4%)	686 (5.3%)	177 (5.9%)
Northern Europe	4461 (28.1%)	3701 (28.7%)	760 (25.5%)
South and Central America	240 (1.5%)	164 (1.3%)	76 (2.5%)
South and East Asia	1549 (9.7%)	1126 (8.7%)	423 (14.1%)
Southern Europe	3276 (20.6%)	2745 (21.2%)	531 (17.8%)
Western Asia and North Africa	350 (2.2%)	286 (2.2%)	64 (2.1%)
Maternal education level			
Low*	2130 (13.4%)	1637 (12.7%)	493 (16.5%)
Medium or high†	12 518 (78.8%)	10 324 (80.0%)	2194 (73.6%)
Unknown	1245 (7.8%)	950 (7.4%)	295 (9.9%)

(Table 1 continues in next column)

	Overall (n=15 893)	Antiseizure monotherapy (n=12 911)	Antiseizure polytherapy (n=2982)
(Continued from previous column)			
Type of maternal epilepsy			
Generalised	6854 (43.1%)	5799 (44.9%)	1055 (35.3%)
Focal	8180 (51.5%)	6364 (49.3%)	1816 (60.9%)
Undetermined	514 (3.2%)	451 (3.5%)	63 (2.1%)
Unknown	345 (2.2%)	297 (2.3%)	48 (1.6%)
Occurrence of seizures during pregnancy			
Any seizure type	5664 (35.6%)	3941 (30.5%)	1723 (57.8%)
Tonic-clonic seizures‡	2557 (16.1%)	1746 (13.5%)	811 (27.2%)
Other seizure types‡	4318 (27.2%)	2946 (22.8%)	1372 (46.0%)
Total number of seizures§			
No seizures	10 229 (64.4%)	8970 (69.5%)	1259 (42.2%)
1–9 seizures	3334 (21.0%)	2438 (18.9%)	896 (30.0%)
≥10 seizures	1938 (12.2%)	1200 (9.3%)	738 (24.7%)
Unknown	392 (2.5%)	303 (2.3%)	89 (3.0%)
Primigravida			
Yes	7194 (45.3%)	5821 (45.1%)	1373 (46.0%)
No	8679 (54.6%)	7072 (54.8%)	1607 (53.9%)
Unknown	20 (0.1%)	18 (0.1%)	2 (0.1%)
Maternal tobacco smoking (any use during pregnancy)			
Yes	1775 (11.2%)	1383 (10.7%)	392 (13.1%)
No	14 060 (88.5%)	11 479 (88.9%)	2581 (86.5%)
Unknown	58 (0.4%)	49 (0.4%)	9 (0.3%)
Maternal alcohol consumption (any use during pregnancy)			
Yes	1509 (9.5%)	1279 (9.9%)	230 (7.7%)
No	14 317 (90.1%)	11 573 (89.6%)	2744 (92.0%)
Unknown	67 (0.4%)	59 (0.5%)	8 (0.3%)
Folic acid intake			
Preconception and after conception¶	5291 (33.3%)	4360 (33.8%)	931 (31.2%)
After conception only	5331 (33.5%)	4275 (33.1%)	1056 (35.4%)
No intake or underdosed**	3695 (23.2%)	3032 (23.5%)	663 (22.2%)
Unknown	1576 (9.9%)	1244 (9.6%)	332 (11.1%)

(Table 1 continues in next column)

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

29 900 participants with pregnancies were enrolled up to Nov 15, 2023, of whom 15 893 met eligibility criteria (figure 1). Of those, 12 911 (81.2%) were exposed to antiseizure monotherapy and 2982 (18.8%) to polytherapy. The most common monotherapies were lamotrigine (n=4672; 36.1% of all monotherapies),

	Overall (n=15 893)	Antiseizure monotherapy (n=12 911)	Antiseizure polytherapy (n=2982)
(Continued from previous column)			
Additional information			
Parental history of major congenital malformations			
Positive	167 (1.0%)	133 (1.0%)	34 (1.1%)
Negative	14 809 (93.2%)	12 082 (93.6%)	2727 (91.4%)
Unknown	917 (5.8%)	696 (5.4%)	221 (7.4%)
Paternal education level			
Low*	2301 (14.5%)	1820 (14.1%)	481 (16.1%)
Medium or high†	11 984 (75.4%)	9847 (76.3%)	2137 (71.7%)
Unknown	1608 (10.1%)	1244 (9.6%)	364 (12.2%)

Data are mean (SD) or n (%). The category unknown refers to missing data. Sex and ethnicity, as categorised, were established by the reporting physician through interview with the mother and medical record review. EURAP=International Registry of Antiepileptic Drugs and Pregnancy. SGA=small-for-gestational age. *≤9 years of education. †>9 years of education. ‡Some mothers had both tonic-clonic seizures and other seizure types during pregnancy, explaining why the sum of the counts for the two seizure categories exceed those for any seizure type. §In EURAP, seizures are quantified in each trimester into one of six predefined categories (no seizures, less than one per month, monthly, weekly, more than weekly, and daily). To compute total number of seizures in a given trimester, number of seizures per trimester was conservatively estimated as one when seizures were reported to have occurred 'less than one per month' in that trimester; three when seizures were reported to have occurred 'monthly'; 12 when seizures were reported to have occurred 'weekly'; 24 seizures when seizures were reported to have occurred 'more than weekly'; and 90 when seizures were reported to have occurred 'daily'. Third-trimester seizure counts were adjusted in pregnancies where delivery differed from a 90-day trimester, rounding down to the nearest integer. The total number of seizures across the pregnancy was then calculated by adding up the seizures in each trimester, and the three total number of seizures categories (no seizures, one to nine seizures, and ten or more seizures) were established to ensure adequate numbers per category. ¶Folic acid supplementation of a dose ≥0.4 mg per day, initiated at least 3 months before conception and maintained throughout the first trimester at least. ||Folic acid supplementation of a dose ≥0.4 mg per day, initiated any time after conception. **No folic acid supplementation or any other supplementation.

Table 1: Characteristics of the cohort included in the analysis

carbamazepine (n=2797; 21.7%), valproic acid (n=1829; 14.2%), levetiracetam (n=1809; 14.0%), oxcarbazepine (n=557; 4.3%), phenobarbital (n=431; 3.3%), topiramate (n=248; 1.9%), and phenytoin (n=180; 1.4%). Other antiseizure medications accounted for 388 (3.0%) monotherapy exposures and were included only in the comparison of fetal growth indicators between monotherapy and polytherapy. The top three of the ten most common polytherapies were lamotrigine–levetiracetam (n=470; 15.8% of all polytherapies), lamotrigine–valproic acid (n=258; 8.6%), and carbamazepine–levetiracetam (n=173; 5.8%; appendix p 12). The characteristics of the population are shown in table 1.

Birthweight centile of offspring exposed to antiseizure polytherapy was lower than that of offspring exposed to monotherapy (adjusted *b* −2.74 [95% CI −4.22 to −1.26]; table 2). Compared with monotherapy, polytherapy was also associated with a higher risk of the outcomes SGA (adjusted OR 1.48 [95% CI 1.29 to 1.70]), severe SGA

(1.49 [1.22 to 1.83]), and low birthweight (1.50 [1.15 to 1.95]). Findings were largely unchanged after additional adjustment for parental educational levels (appendix pp 16–17), greater stratification of maternal folate intake (appendix pp 18–19), and additional adjustment for total number of seizures during pregnancy (appendix pp 20–21), and when limiting the analyses to offspring of mothers who were seizure-free during pregnancy (appendix pp 22–23).

Birthweight centile decreased and risk of SGA (but not severe SGA or low birthweight) increased with increasing number of concomitantly used antiseizure medications (figure 2; appendix p 29).

Among antiseizure medication monotherapies, carbamazepine, levetiracetam, oxcarbazepine, phenobarbital, topiramate, and valproic acid were associated with lower birthweight centiles (adjusted *b* −2.51 [95% CI −4.38 to −0.63] to −11.93 [−16.72 to −7.15]) and a 28% to 145% increased risk of SGA compared with lamotrigine (figure 3; appendix p 30). These effects were most prominent with topiramate, phenobarbital, and oxcarbazepine, which were also associated with an 83% (phenobarbital), an 86% (oxcarbazepine), and a 175% (topiramate) increased risk of severe SGA and a 94% (phenobarbital), a 143% (oxcarbazepine), and a 392% (topiramate) increased risk of low birthweight. The absolute prevalence estimates were 25.4–33.0% for SGA, 11.4–14.4% for severe SGA, and 8.1–11.9% for low birthweight across offspring exposed to topiramate, phenobarbital, or oxcarbazepine, compared with an absolute prevalence of 14.6% for SGA, 5.1% for severe SGA, and 4.5%, for low birthweight among offspring exposed to lamotrigine. Phenytoin exposure had an opposite effect on fetal growth, being associated with a higher birthweight centile (adjusted *b* 8.04 [95% CI 2.81 to 13.27]) compared with lamotrigine exposure.

There was a weak direct association between dose and birthweight centile for lamotrigine and a much stronger and direct association between dose and risk of SGA for oxcarbazepine (appendix p 24). For oxcarbazepine, doses higher than 1700 mg per day carried a 3.5-fold higher risk of SGA than doses less than 1100 mg per day (appendix p 25).

A total of 12 517 offspring (78.8% of the entire cohort) were exposed only to carbamazepine, lamotrigine, levetiracetam, phenytoin, or valproic acid (11 287 to monotherapy and 1230 to combinations of these antiseizure medications). In this subset, which excluded the antiseizure medications most prominently associated with poor fetal growth, there were no significant differences between monotherapy and polytherapy across fetal growth indicators (appendix pp 26–27). Among the most common polytherapies, the combination of carbamazepine and levetiracetam was associated with a lower birthweight centile (adjusted *b* −6.27 [95% CI −12.03 to −0.50]) and an 86% increased

	<i>b</i> (95% CI)	OR (95% CI)		
	Birthweight centile	SGA	Severe SGA	Low birthweight*
Antiseizure polytherapy	-2.74 (-4.22 to -1.26)	1.48 (1.29 to 1.70)	1.49 (1.22 to 1.83)	1.50 (1.15 to 1.95)
Year of pregnancy	0.06 (-0.04 to 0.15)	0.99 (0.98 to 1.00)	0.98 (0.97 to 1.00)	1.00 (0.98 to 1.01)
Male offspring	8.65 (7.44 to 9.87)	0.58 (0.52 to 0.66)	0.60 (0.50 to 0.72)	0.65 (0.52 to 0.82)
Region of enrolment (ref: Western Europe)				
Australia and New Zealand	4.04 (1.65 to 6.44)	0.76 (0.60 to 0.96)	0.80 (0.58 to 1.12)	0.85 (0.55 to 1.33)
Eastern Europe	-0.65 (-2.83 to 1.54)	0.89 (0.72 to 1.11)	0.63 (0.41 to 0.97)	0.69 (0.41 to 1.15)
Northern Europe	4.32 (2.69 to 5.94)	0.82 (0.70 to 0.97)	0.76 (0.59 to 0.97)	0.82 (0.60 to 1.12)
South and Central America	-0.01 (-3.63 to 3.61)	0.74 (0.48 to 1.14)	0.73 (0.38 to 1.42)	0.98 (0.54 to 1.77)
South and East Asia	-19.05 (-21.72 to -16.39)	4.14 (3.34 to 5.12)	3.99 (2.98 to 5.34)	3.37 (2.33 to 4.88)
Southern Europe	-7.43 (-9.30 to -5.56)	1.48 (1.26 to 1.74)	1.44 (1.13 to 1.84)	1.17 (0.86 to 1.57)
Western Asia and North Africa	-6.04 (-10.91 to -1.17)	1.04 (0.70 to 1.54)	1.29 (0.72 to 2.31)	1.31 (0.61 to 2.84)
Maternal age at conception, years	0.08 (-0.03 to 0.19)	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.02)
Parental history of major congenital malformations	-1.96 (-6.77 to 2.85)	1.56 (0.99 to 2.45)	1.98 (1.07 to 3.66)	1.84 (0.85 to 3.95)
Type of maternal epilepsy (ref: generalised)				
Focal	-1.21 (-2.33 to -0.08)	1.14 (1.02 to 1.28)	1.24 (1.04 to 1.47)	1.31 (1.05 to 1.64)
Undetermined	0.65 (-2.01 to 3.32)	1.23 (0.93 to 1.63)	1.39 (0.91 to 2.11)	0.87 (0.47 to 1.60)
Tonic-clonic seizures during pregnancy	-1.36 (-2.75 to 0.02)	1.15 (1.00 to 1.31)	1.19 (0.99 to 1.45)	1.27 (0.98 to 1.64)
Other seizure types during pregnancy	-0.24 (-1.29 to 0.82)	0.94 (0.84 to 1.05)	0.98 (0.84 to 1.13)	1.03 (0.84 to 1.26)
Primigravida	-5.56 (-6.77 to -4.35)	1.41 (1.25 to 1.59)	1.33 (1.12 to 1.58)	1.43 (1.13 to 1.82)
Maternal tobacco smoking during pregnancy	-6.28 (-8.13 to -4.42)	1.70 (1.43 to 2.03)	1.77 (1.38 to 2.27)	1.65 (1.18 to 2.29)
Maternal alcohol consumption during pregnancy	0.44 (-1.00 to 1.87)	0.92 (0.78 to 1.08)	1.04 (0.83 to 1.31)	0.96 (0.68 to 1.34)
Folate (ref: no intake or underdosed)				
Preconception and after conception	-0.82 (-2.11 to 0.46)	1.01 (0.90 to 1.15)	0.95 (0.79 to 1.13)	0.97 (0.76 to 1.22)
After conception only	-0.43 (-1.68 to 0.83)	0.97 (0.86 to 1.10)	0.85 (0.70 to 1.04)	0.72 (0.54 to 0.95)

Data are point estimates (95% CI). The widths of 95% CIs have been adjusted for family-wise multiplicity with a false discovery rate of $q=5\%$. Findings were obtained from four separate models, one for each indicator of fetal growth. A generalised linear mixed model was used for birthweight centile and applied to the entire study cohort ($n=15\,893$). Logistic regression models were used for SGA, severe SGA, and low birthweight; owing to failure of model convergence, logistic regression models were run on a subset comprising a single offspring (the first recorded in EURAP in case of multiple offspring) for each mother ($n=13\,728$; appendix pp 13–14). All models were adjusted for calendar year of pregnancy, offspring sex, geographical region, maternal age, parental history of major congenital malformations, maternal epilepsy type, occurrence of tonic-clonic seizures during pregnancy, occurrence of other seizure types during pregnancy, primigravida status, tobacco smoking during pregnancy, alcohol consumption during pregnancy, and folate intake. The model for low birthweight was also adjusted for gestational age. *b*=unstandardised model coefficient. EURAP=International Registry of Antiepileptic Drugs and Pregnancy. OR=odds ratio. SGA=small-for-gestational age. *Model for low birthweight was also adjusted for gestational age (weeks): OR 0.44 (95% CI 0.41 to 0.47).

Table 2: Relationship of antiseizure regimen (monotherapy vs polytherapy) and other factors with different indicators of fetal growth

risk of SGA (adjusted OR 1.86 [95% CI 1.06 to 3.25]) compared with lamotrigine monotherapy (appendix p 28). As for the other two most common antiseizure medication combinations, no differences in birthweight centile were found between offspring exposed to lamotrigine monotherapy and those exposed to the combination of lamotrigine with levetiracetam (adjusted *b* 0.19 [95% CI -2.67 to 3.06]) or valproic acid (0.11 [-3.59 to 3.82]). The lamotrigine–levetiracetam and lamotrigine–valproic acid combinations also did not differ from lamotrigine monotherapy across any of the other fetal growth indicators.

With respect to other risk factors for poor fetal growth, birthweight centile was significantly reduced in female offspring and when the mother was a primigravida, a smoker, or had focal epilepsy (table 2). The same factors were also associated with an increased risk of SGA, severe SGA, and low birthweight. An increased risk of SGA was additionally associated with occurrence of

tonic-clonic seizures during pregnancy, and an increased risk of severe SGA with a parental history of major congenital malformations. A reduction in the risk of low birthweight was associated with post-conception folate intake compared to no or underdosed folate supplementation. Birthweight centile and risk of SGA, severe SGA, and low birthweight were also influenced by geographical region (table 2).

Discussion

This cohort study is, to our knowledge, the largest prospective investigation of poor fetal growth after prenatal exposure to antiseizure medication therapy. We evaluated four different indicators of fetal growth (birthweight centile, SGA, severe SGA, and low birthweight), and we controlled for a wide set of potential confounders. We found that birthweight centile (primary endpoint) was significantly lower in offspring exposed to antiseizure medication polytherapy than in those

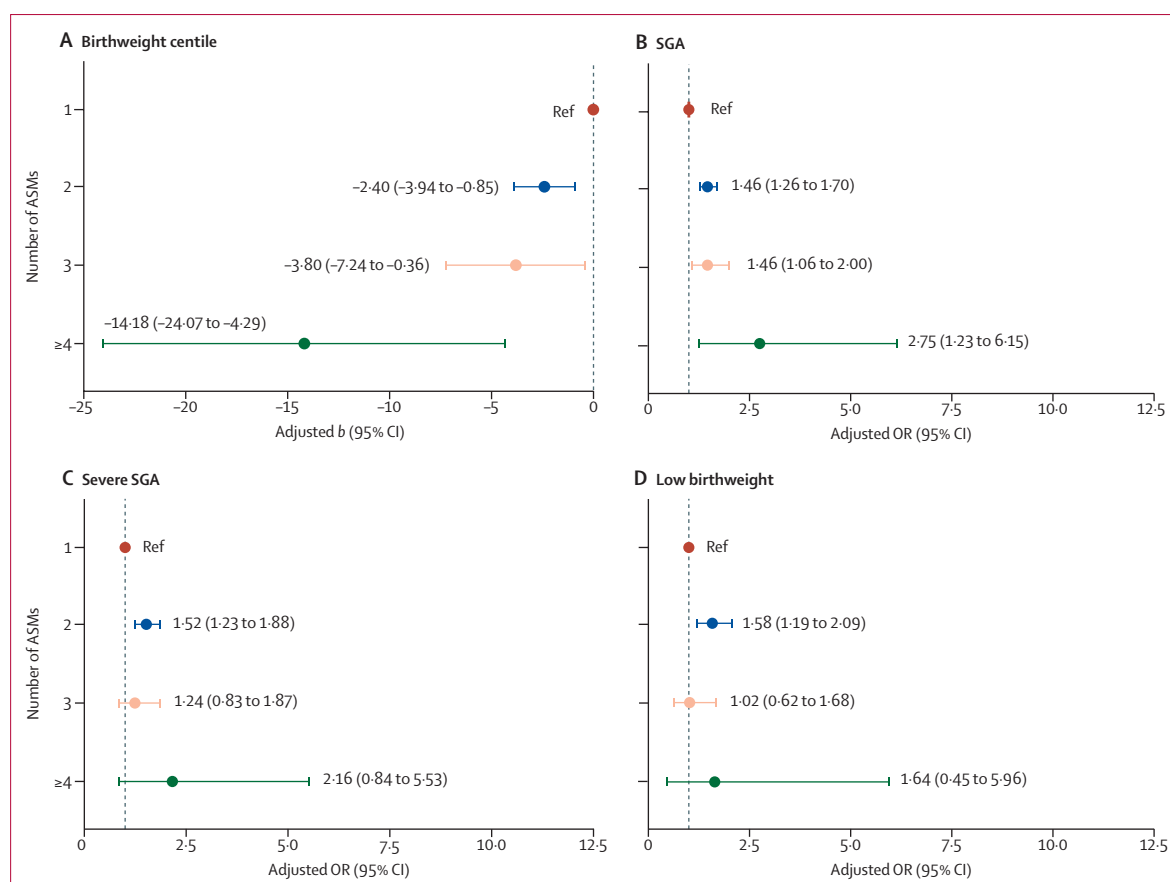


Figure 2: Strength of association between number of concomitantly used ASMs and indicators of poor fetal growth

(A) Adjusted *b* with 95% CIs (error bars) for birthweight centile in offspring exposed to one to four or more ASMs, with monotherapy exposure as reference. Adjusted OR with 95% CIs (error bars) for SGA (B), severe SGA (C), and low birthweight (D) in offspring exposed to one to four or more antiseizure medications, with monotherapy exposure as reference. *b* and ORs, with their 95% CIs, were computed in models adjusted for the clinical and demographic variables (table 2). ASM=antiseizure medication. *b*=unstandardised model coefficient. OR=odds ratio. SGA=small for gestational age.

exposed to monotherapy, and similar differences were present across all other indicators. The robustness of these findings was supported by the sensitivity analysis, which adjusted for greater stratification of folate supplementation or additional potential confounders such as parental educational status and seizure control. We also describe a previously unreported finding of lower birthweight centile and higher SGA risk with increasing number of concomitantly used antiseizure medications, an observation highly suggestive of a causal relation. The assessed outcomes are both important biologically (given that falling birthweight centile is associated with a stepwise increase in perinatal risk and long-term adverse outcomes, even among those not classified as SGA^{28–31}) and clinically (given that infants classified as SGA and severely SGA are at highest absolute risk, warranting closer surveillance during pregnancy and after birth). The consistency of findings across all key outcomes supports the plausibility and validity of our results. Evidence for a causality relation between prenatal antiseizure medication exposure and poor fetal growth is reinforced by the

demonstration that outcomes differed across individual antiseizure medications, the highest risk being associated with topiramate, phenobarbital, and oxcarbazepine. Furthermore, for oxcarbazepine, the risk was dose dependent. Notably, our exploration of associations with dose was based on the treatment recorded at conception, and it would be interesting in future studies to assess potential correlations with the cumulative dose taken throughout pregnancy.

A higher prevalence of SGA after exposure to antiseizure polytherapy compared with monotherapy has been reported in a study of data from the prospective North American Antiepileptic Drug Pregnancy Registry (NAAPR),¹⁹ and by a 2024 retrospective population-based study,¹³ which analysed administrative health-care databases from five Nordic countries. The 2024 study, however, could not control for the presence or absence of seizures and epilepsy type, whereas the NAAPR study did not control for seizure type and epilepsy type. Seizures during pregnancy represent an independent risk factor for poor fetal growth,¹⁸ but the role of seizure type has not

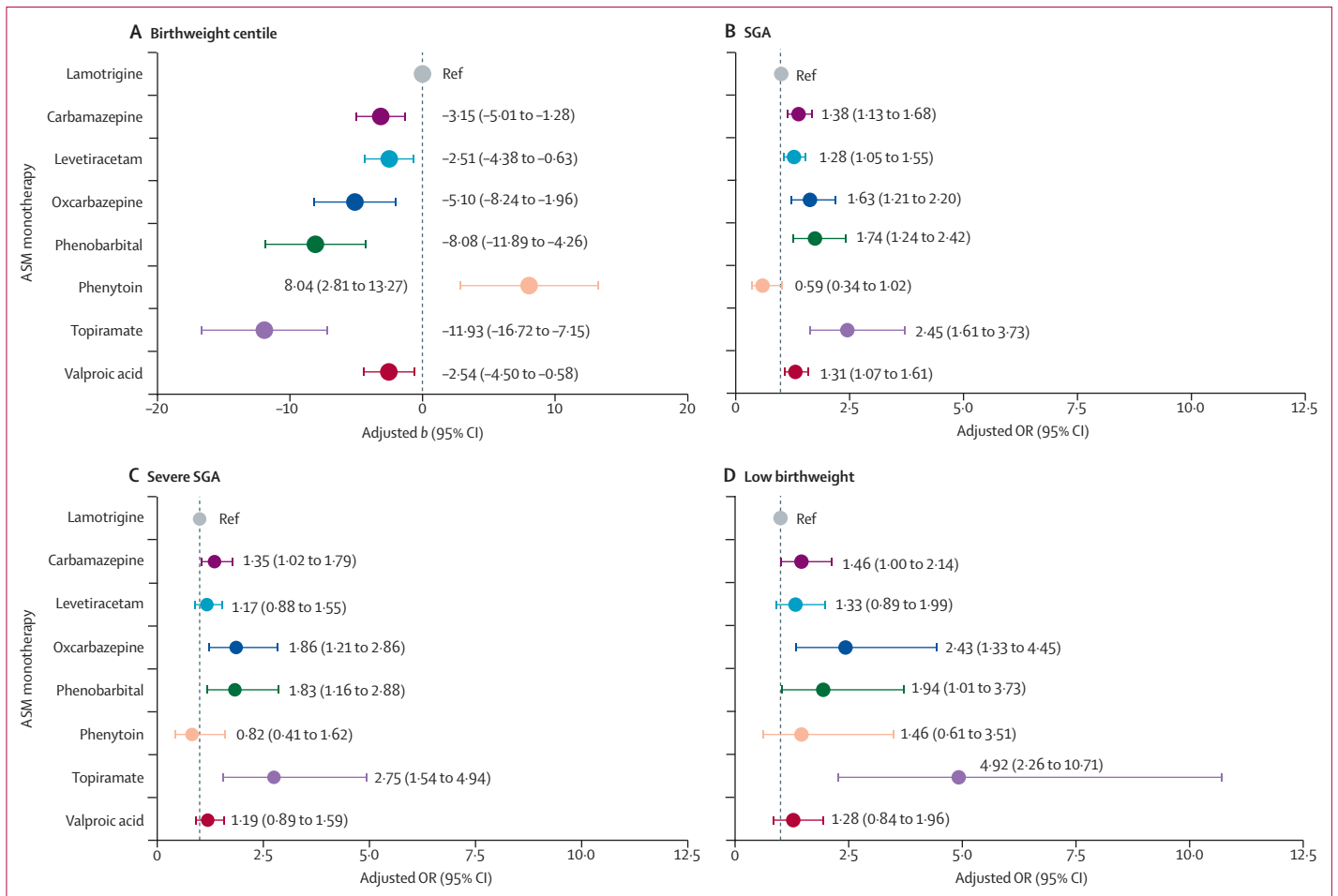


Figure 3: Strength of association between individual antiseizure medication monotherapies and different indicators of fetal growth

(A) Adjusted unstandardised model coefficient b with 95% CIs (error bars) for birthweight centile in offspring exposed to individual antiseizure medication monotherapies, with lamotrigine as reference. Adjusted OR with 95% CIs (error bars) for SGA (B), severe SGA (C), and low birthweight (D) in offspring exposed to individual antiseizure medication monotherapies, with lamotrigine as reference. b and ORs, with their 95% CIs, were computed in models adjusted for the clinical and demographic variables (table 2). ASM=antiseizure medication. b =unstandardised model coefficient. OR=odds ratio. SGA=small for gestational age.

been adequately investigated. We found tonic-clonic seizures during pregnancy to be associated with an increased risk of SGA, whereas their association with lower birthweight centile and increased risks of severe SGA and low birthweight only approached statistical significance. A 2025 small prospective study from China also suggested an association between tonic-clonic seizures during pregnancy and low birthweight.²⁰ Collectively, these results indicate a deleterious effect of tonic-clonic seizures on fetal growth, which might be mediated by placental insufficiency.³² Besides seizure type, epilepsy type was identified in our analysis as an additional independent risk factor, as evidenced by lower birthweight centile and increased risk of SGA, severe SGA, and low birthweight in offspring born to mothers with focal epilepsy compared with those born to mothers with generalised epilepsy. This finding might be explained by women with focal epilepsy possibly having more severe disease or underlying causes associated with unmeasured

confounding factors. Another interesting and novel finding was that a parental history of major congenital malformations was associated with an almost doubled risk of severe SGA. Coupled with evidence of a three times greater risk of major congenital malformations when a parental history of major congenital malformations is present (compared with its absence),³³ this finding highlights the importance of genetic predisposition and has implications for preconception counselling.

Previously reported data on comparative risks associated with individual antiseizure medications are conflicting, probably because of confounders and the small size of the assessed subcohorts.^{11–15,19} In agreement with NAAAPR,¹⁹ we found that topiramate and phenobarbital were associated with the highest risk. In the NAAAPR study,¹⁹ zonisamide was also identified as high risk, which we could not confirm or refute owing to the small number of zonisamide monotherapy exposures ($n=29$) in EURAP. We also found a prominent and

dose-dependent risk in offspring exposed to oxcarbazepine. Topiramate and oxcarbazepine were also the antiseizure medications associated with the highest risk in the retrospective population-based Nordic study.¹³ Compared with lamotrigine, the risk of poor fetal growth after exposure to carbamazepine, valproic acid, and levetiracetam was relatively small. Conversely, exposure to phenytoin was associated with a larger birthweight centile compared with lamotrigine. Interestingly, in the NAAPR study, phenytoin was also the sole antiseizure medication with a lower SGA risk than lamotrigine, even though the difference was not significant. The mechanisms underlying the association between antiseizure medication exposure and poor fetal growth are unclear, but differences in risk across antiseizure medications suggest that mechanisms also differ. For example, the risks of topiramate exposure could be linked to its weight loss-inducing properties,³⁴ whereas the apparent risk reduction by phenytoin could result from its ability to cause hyperglycaemia.³⁵ Because oxcarbazepine and carbamazepine share similar antiseizure mechanisms, the greater risk of poor fetal growth with oxcarbazepine exposure is probably explained by differences between these drugs in ancillary pharmacological effects, including effects on the endocrine system.³⁶ Mechanisms underlying poor fetal growth associated with specific antiseizure medications represent an interesting area for further research. The likely heterogeneity of these mechanisms raises the question of whether perinatal and long-term consequences of poor fetal growth also vary with type of antiseizure medication exposure, a possibility that should also be investigated in future studies.

The prevalence of major congenital malformations in offspring exposed to antiseizure polytherapy differs depending on the type of antiseizure medications being used.³⁷ The observation that the risk of poor fetal growth differs prominently across antiseizure medication monotherapies suggests that similar differences in risk might also occur between specific antiseizure medication combinations. Indeed, when limiting our analyses to offspring exposed to low-risk antiseizure medications—that is, carbamazepine, lamotrigine, levetiracetam, phenytoin, or valproic acid—fetal growth indicators no longer differed between polytherapy and monotherapy exposures. Moreover, when the most common polytherapies were assessed relative to lamotrigine monotherapy, we identified increased risks for poor fetal growth for carbamazepine–levetiracetam, but not for lamotrigine–levetiracetam or lamotrigine–valproic acid. Collectively, these findings indicate that, similar to the risk of major congenital malformations, the risk of poor fetal growth varies with type of antiseizure medications used in combination, rather than being due to polytherapy per se.

Strengths of our study include enrolment of a large cohort from five different continents, and the accurate prospective collection of a wide array of variables by

treating physicians, rather than through patient interviews, medical records, or proxy databases. The accurate collection of many variables allowed for the analysis of different fetal growth indicators and adjustment for potential confounders. As for limitations, the study was observational (non-randomised), was not population based, had limited representation of ethnicities other than White or Asian, and did not include cohorts exposed to antiseizure medications for indications other than epilepsy. Although the identified risks are likely to also apply to antiseizure medication exposure for other indications, further large prospective studies would be desirable to address this. Another limitation is that we did not include a control group of pregnancies not exposed to antiseizure medication, because withholding antiseizure medication from women with active epilepsy is not generally an option, and the key clinical question is not whether treatment can be avoided, but what treatment is safest. Although we controlled for many confounders, we could not control for maternal weight or nutritional status, which are not recorded in EURAP. Our analytical approach adjusted for potential confounders using a traditional regression approach, which assumes no interaction between antiseizure medication exposure and covariates. Future research in larger cohorts might consider applying other causal inference methods, such as inverse probability weighting or trial emulation. Last, we evaluated SGA using a standard reference, rather than country-specific centiles. Although we did adjust for the effect of geographical region, the accuracy of absolute SGA values was inherently limited. This limitation should not affect the validity of comparisons across exposure groups but should be considered when making comparisons with other studies. The overall prevalence of SGA in our population (20%) was similar to that reported previously (17–22%) in offspring of antiseizure medication-treated women with epilepsy,¹⁸ although the prevalence estimated by the NAAPR was lower (11%).¹⁹

Overall, our findings are important for clinical management. In the absence of specific data on the health implications of poor fetal growth in antiseizure medication-exposed offspring, it would be reasonable to assume that the perinatal and long-term morbidity and mortality risks associated with poor fetal growth in the general population also apply to the antiseizure medication-exposed population. Consideration of these risks and their association with the type of antiseizure medication exposure should, similar to major congenital malformations and neurodevelopmental disorders, be part of routine preconception counselling and clinical decision making. For women with epilepsy, any change in antiseizure medication therapy aimed at protecting fetal health should generally be done preconception and take into consideration not only maternal and fetal risks related to antiseizure medication exposure, but also those associated with potential loss or worsening of seizure control.

Contributors

PP, DB, EP, and TT conceived the study. All authors contributed equally to the study design. BMK and DB verified the data. CBM performed the statistical analysis, with assistance from DB and AB-N. All authors had full access to the data and contributed equally to the interpretation of the data. PP, CBM, AB-N and EP drafted the first version of the manuscript, and all authors contributed to the revision of the initial draft and the finalisation of the submitted manuscript. All authors take responsibility for the decision to submit for publication.

Declaration of interests

PP received speaker honoraria or consultancy fees to his institution from Biocodex, Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, outside of the submitted work. He is Deputy Editor for *Epilepsia Open*. CBM has received conference travel support and/or speaker fees from Merck, Novartis, and Biogen, outside of this submitted work. He is an Associate Editor for the *British Journal of Psychiatry Open*. TK served on scientific advisory boards or as a consultant for MS International Federation and World Health Organisation, Therapeutic Goods Administration, BMS, Roche, Janssen, Genzyme, Novartis, Merck, and Biogen; received conference travel support and/or speaker honoraria from WebMD Global, Merck, Sandoz, Novartis, Biogen, Roche, Eisai, Genzyme, Teva, and BioCSL; and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene, and Merck, outside of the submitted work. SA has received speaker honoraria from Eisai. JC has received honoraria from UCB-Pharma, GlaxoSmithKline, Janssen-Cilag, Sanofi-Synthelabo, Pfizer, and Eisai to attend advisory boards, present lectures and tutorials, and to attend conferences, and received donations from UCB-Pharma, GlaxoSmithKline, Janssen-Cilag, Sanofi-Synthelabo, Pfizer, and Eisai to fund research. AS has received consulting or lecture fees from Jazz Pharmaceuticals, Angelini Pharma, and UCB Nordic. EP received speaker's or consultancy fees from Eisai, GRIN Therapeutics, SK Life Science, Sun Pharma, Takeda, UCB Pharma, and Xenon Pharma, and royalties from Wiley and Elsevier, outside of the submitted work. TT has received speaker honoraria to his institution from Angelini, Eisai, and UCB. All other authors declare no competing interests.

Data sharing

Summary statistics supporting the findings of this study are available upon reasonable request. The request should be directed to the corresponding author via email (piero.pericca@unimelb.edu.au), and will then be assessed by the Central Project Commission of EURAP. Owing to ethical restrictions and privacy protection regulations, we are unable to publicly share individual-level data.

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