

# Antiepileptic Drugs in Pregnancy and Duration of Pregnancy, Birth Weight, Length, and Head Circumference

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## DISCLOSURES

Brian D'Onofrio, Anna Sara Oberg, and Catarina Almqvist received grant funds from the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework grant no. 340-2013-5867 for research. Sonia Hernandez-Diaz received honoraria as a consultant from Roche and UCB; as an investigator from Pfizer, GSK, and Lilly; and salary support for work in the North American Antiepileptic Drugs Pregnancy Registry from multiple companies. Andrea Margulis, Estel Plana, and Ken Rothman report funds paid to employer by multiple companies: RTI Health Solutions, part of RTI International, is an independent nonprofit research organization that conducts work for government and other organizations including pharmaceutical companies; this work was internally funded.

## BACKGROUND

- Antiepileptic drugs (AEDs) have been linked to reduced pregnancy duration and fetal growth restriction.<sup>1,2</sup>
- Dose-response effects have not been well characterized for these outcomes; such effects are known for valproic acid and other AEDs with birth defects.<sup>3</sup>

## OBJECTIVE

- To explore the effect of maternal use of individual AEDs in pregnancy on pregnancy duration, birth weight, birth length, and head circumference, and possible dose-response effects on these outcomes.

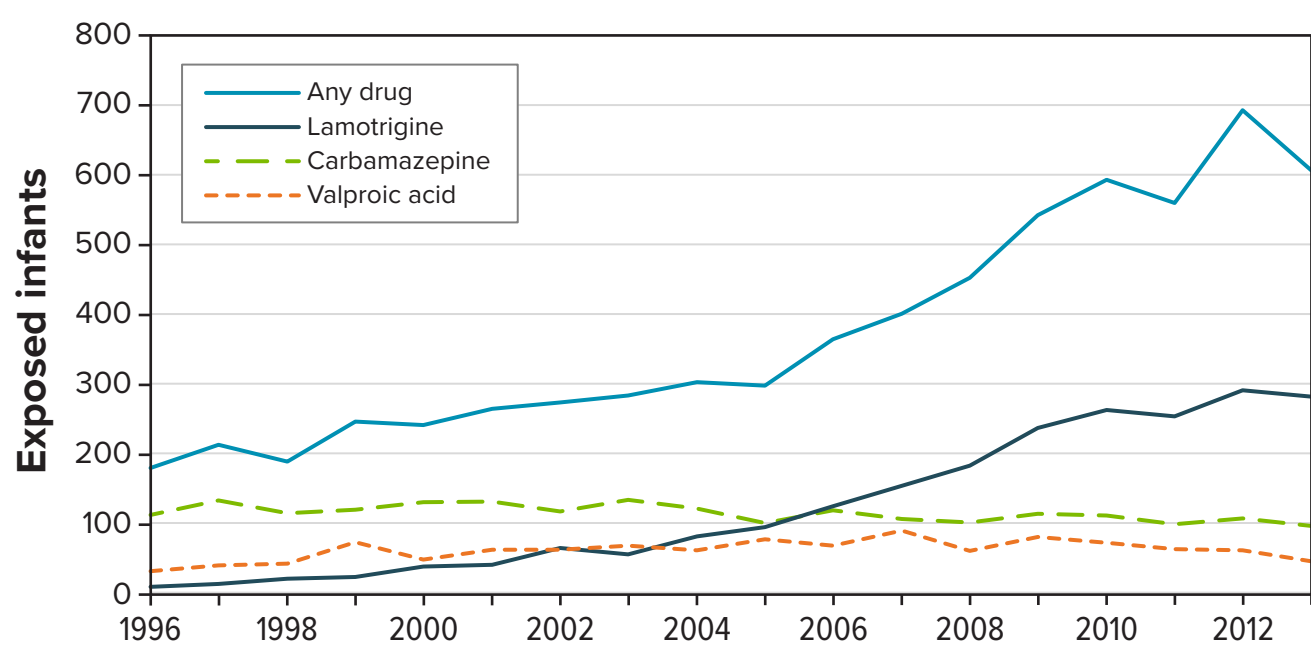
## METHODS

- We conducted a comparative-safety cohort study using nationwide Swedish Register data.
- **Study population:** All women exposed to AEDs in pregnancy who had a live birth at gestational age 24 to 42 completed weeks in the years 1996 through 2013 and their newborn infants. Infants from either single or multiple pregnancies and infants with congenital malformations were included. Pregnancies in women who immigrated fewer than 12 months before pregnancy and infants with chromosomal abnormalities were excluded. All eligible pregnancies per woman were included.
- **Exposure:** Carbamazepine, valproic acid, and lamotrigine (used as reference). Maternal use was ascertained from maternal self-report and dispensed prescriptions during pregnancy. Mean daily dose in pregnancy was calculated from dispensed prescriptions in the years 2006 through 2013.
- **Characteristics of the study population:** Demographic characteristics, medical conditions, and medications used were ascertained from prenatal care records, hospitalization records, outpatient specialist visits, and dispensed prescriptions.
- **Endpoints:** Duration of pregnancy, birth weight, length, and head circumference.
- **Statistical analyses:** We used linear regression to assess the associations of interest, adjusting for key potential confounders (see the list below Table 2). In AED-specific dose analyses, we compared the association of high dose (top tertile of mean daily dose in pregnancy) versus low dose (bottom tertile) of each AED with the same outcomes, adjusting for the same variables.

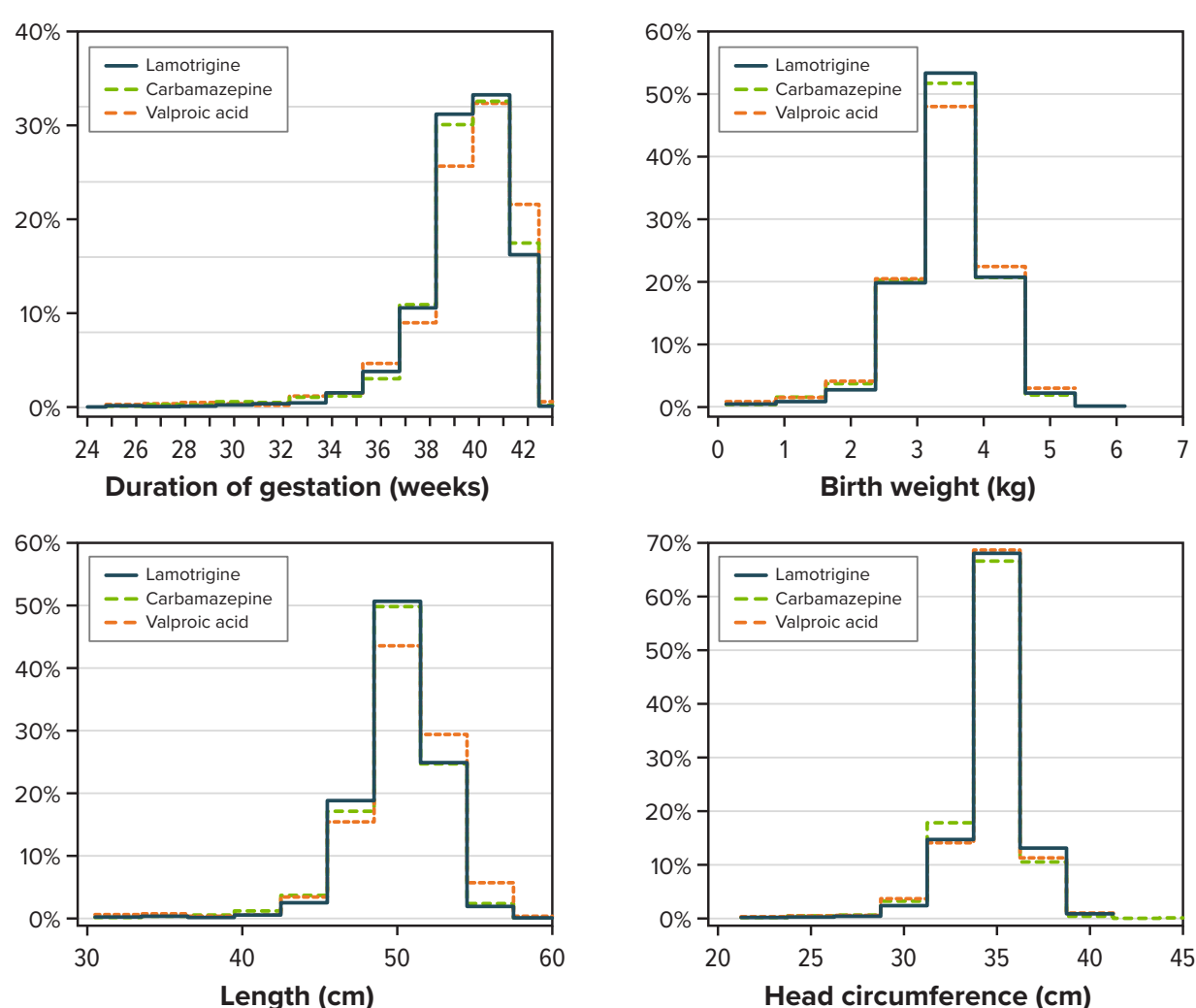
## RESULTS

- The study cohort had 6,720 AED-exposed infants. AED use in pregnancy increased over the study period (Figure 1). Table 1 shows the characteristics of the study population by exposure drug.
- Results are shown in Figure 2 (unadjusted) and Table 2 (adjusted).

**Figure 1. Use of AEDs in Pregnancy**



**Figure 2. Duration of Pregnancy, Birth Weight, Length, and Head Circumference**



**Table 1. Characteristics of the Study Population and Mean Daily Dose by Drug**

Characteristic	Lamotrigine	Carbamazepine	Valproic Acid
Number of exposed women	1,757	1,529	809
Number of exposed offspring	2,254	2,095	1,137
Maternal age at delivery (years)			
24 or younger	427 (18.9%)	249 (11.9%)	206 (18.1%)
25-29	691 (30.7%)	626 (29.9%)	350 (30.8%)
30-34	721 (32.0%)	728 (34.7%)	374 (32.9%)
35 or older	415 (18.4%)	492 (23.4%)	207 (18.2%)
Mother's country of origin			
Nordic countries	2,040 (90.5%)	1,812 (86.5%)	995 (87.5%)
Other European countries	86 (3.8%)	72 (3.4%)	59 (5.2%)
Asia	82 (3.6%)	128 (6.1%)	60 (5.3%)
Others	46 (2.0%)	83 (4.0%)	23 (2.0%)
Maternal education: completed 13 years or more	826 (36.6%)	717 (34.2%)	364 (32.0%)
Mother lives with child's father	2,001 (88.8%)	1,911 (91.2%)	1,044 (91.8%)
Early-pregnancy BMI (kg/m <sup>2</sup> )			
Lower than 18.5	44 (2.0%)	33 (1.6%)	22 (1.9%)
18.5 to less than 25	1,272 (56.4%)	1,273 (60.8%)	616 (54.2%)
25 to less than 30	595 (26.4%)	500 (23.9%)	318 (28.0%)
30 or higher	343 (15.2%)	289 (13.8%)	181 (15.9%)
Smoker in current pregnancy	386 (17.1%)	258 (12.3%)	211 (18.6%)
Alcohol dependence	123 (5.5%)	38 (1.8%)	25 (2.2%)
AED indications/uses			
Epilepsy	1,559 (69.2%)	1,774 (84.7%)	939 (82.6%)
Depression	445 (19.7%)	106 (5.1%)	86 (7.6%)
Bipolar disorder	460 (20.4%)	27 (1.3%)	74 (6.5%)
Other psychiatric disorders	645 (28.6%)	179 (8.5%)	162 (14.2%)
Migraine	224 (9.9%)	105 (5.0%)	62 (5.5%)
Chronic pain	575 (25.5%)	283 (13.5%)	172 (15.1%)
Diabetes (preexisting or gestational)	76 (3.4%)	56 (2.7%)	43 (3.8%)
Hypertension (preexisting or gestational)	100 (4.4%)	100 (4.8%)	65 (5.7%)
High dose (mean, mg/day) <sup>a</sup>	454	905	1,349
Low dose (mean, mg/day) <sup>b</sup>	41	186	211

BMI = body mass index.

<sup>a</sup>Mean dose in top tertile of pregnancy daily dose.

<sup>b</sup>Mean dose in bottom tertile of pregnancy daily dose.

The denominator for calculations is the number of infants. Missing values were observed for maternal education (1.4%), smoking (2.6%), marital status (3.3%), and BMI (9.6%). Thirteen women with no information on BMI but with ICD-10 codes for obesity were included in the BMI category of 30 or more kg/m<sup>2</sup>. Missing values were imputed as the most commonly observed value in the study population.

**Table 2. Antiepileptic Drugs in Pregnancy and Duration of Pregnancy, Birth Weight, Length, and Head Circumference**

Endpoint	Lamotrigine	Carbamazepine	Valproic Acid
<b>Duration of pregnancy (weeks)</b>			
Mean change vs. lamotrigine	N/A	-0.2 (-0.3 to 0.0)	-0.0 (-0.2 to 0.2)
Mean change, high vs. low dose	-0.3 (-0.5 to 0.0)	-0.7 (-1.1 to -0.2)	-0.1 (-0.7 to 0.4)
<b>Birth weight (grams)</b>			
Mean change vs. lamotrigine	N/A	-69 (-112 to -26)	-27 (-79 to 24)
Mean change, high vs. low dose	-11 (-95 to 73)	-170 (-288 to -52)	-82 (-242 to 78)
<b>Birth length (cm)</b>			
Mean change vs. lamotrigine	N/A	-0.3 (-0.5 to -0.1)	0.1 (-0.1 to 0.4)
Mean change, high vs. low dose	0.1 (-0.3 to 0.4)	-0.7 (-1.2 to -0.1)	0.0 (-0.8 to 0.8)
<b>Birth head circumference (cm)</b>			
Mean change vs. lamotrigine	N/A	-0.3 (-0.5 to -0.2)	-0.2 (-0.3 to 0.0)
Mean change, high vs. low dose	0.0 (-0.3 to 0.3)	-0.4 (-0.8 to -0.1)	-0.6 (-1.1 to -0.1)

N/A = not available (lamotrigine was the reference in comparative analyses).

Mean values for high and low doses of each antiepileptic drug are presented in Table 1. Results are adjusted for birth year, maternal age at delivery, education, region of origin, marital status, BMI, smoking in current pregnancy, alcohol dependence, diabetes, hypertension, epilepsy, depression, bipolar disorder, migraine, chronic pain, and other psychiatric disorders.

## CONCLUSIONS

- Relative to lamotrigine, infants exposed to carbamazepine were born 1.5 days earlier on average and were slightly smaller in all assessed dimensions. A dose-response relation was seen for carbamazepine for all outcomes and for valproic acid in relation to head circumference.

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