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ORIGINAL RESEARCH ARTICLE

Effects of Maternal Epilepsy and Antiepileptic Drug Use during Pregnancy on Perinatal Health in Offspring: Nationwide, Retrospective Cohort Study in Finland

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Abstract

Introduction Perinatal health outcomes other than major congenital anomalies in offspring of women with epilepsy (WWE) have not been widely studied, and results of previous studies are conflicting and are mostly based on small numbers. Antiepileptic drugs (AEDs) pass through the placenta and may affect neonatal outcome.

Methods This register-based study is based on information on all pregnancies ending in birth in Finland between 1996 and 2008. The data were obtained from the Finnish national health registers with data linkages based on the unique personal identification numbers. Information on maternal epilepsy diagnosis, AED purchases and other background factors was obtained to evaluate data on perinatal and infant health for all singleton births ($n = 751{,}139$). Drug purchases were considered to be an indicator for drug use. The outcomes included mode of delivery (vaginal birth or Caesarean section), preterm birth, low birth weight, weight for gestational age, low Apgar score, need for respiratory treatment, admission to neonatal care unit, perinatal death and infant death.

Results In total, 4,867 (0.6 %) infants (including live births and stillbirths) were exposed to maternal epilepsy. More than half of the offspring of WWE were exposed to AED ($n = 3{,}067$, 63.0 %) during pregnancy or 1 month prior to and/or during pregnancy, and mostly in monotherapy ($n = 2{,}566$, 83.7 %). The most commonly used AED was carbamazepine ($n = 1{,}292$, 42.1 %; mostly in monotherapy 83.9 %). WWE were more likely to smoke and to have previous miscarriages, lower socioeconomic status, and more co-morbidity than the reference women with no epilepsy diagnosis and no AED use (WOE). A slightly increased risk for most of the perinatal health outcomes was found in offspring of WWE in relation to offspring of WOE (adjusted odds ratio [aOR] 1.19, 95 % CI 1.04–1.36 for low 5-min Apgar score to aOR 2.10, 95 % CI 1.57–2.81 for needing respiratory care). The risks increased by the number of different maternal AEDs used. In relation to offspring of WWE with no AED exposure ($n = 1{,}800$), a slightly increased risk for treatment in a neonatal care unit (aOR 1.48, 95 % CI 1.21–1.82) was observed for offspring of WWE on AED therapy.

Conclusions Offspring of WWE have a slightly increased risk for adverse pregnancy-related and perinatal health outcomes when compared with WOE, and AED exposure further increases the risk. The results should be interpreted with caution, as information on type of epilepsy was unavailable.

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1 Introduction

Approximately 0.7 % of pregnant women in Finland suffer from epilepsy [1] and maternal antiepileptic drug (AED)

treatment is often indicated during pregnancy. The teratogenicity of AEDs has been widely studied, but studies on pregnancy complications and perinatal health outcomes other than major congenital anomalies (MCA) are few. Results from previous studies investigating risks for Caesarean section (CS), low birth weight, small weight for gestational age (SGA), admission to a neonatal care unit and perinatal mortality have been conflicting and mostly based on small numbers [2–11]. Not only epilepsy *per se*, but also AED use may affect the course of pregnancy, perinatal and infant health. AEDs pass the placenta to the fetus and may cause neonatal symptoms due to toxicity or withdrawal. The purpose of this study was to obtain population-based information on pregnancy-related risks and perinatal health risks other than the risk for MCA in women with epilepsy (WWE) on/without AEDs and their offspring. The results are based on the nationwide Drug and Pregnancy study data covering all births in Finland between 1996 and 2008.

2 Materials and Methods

The data were obtained from the Finnish national health registers: the Medical Birth Register (MBR), the Finnish Malformation Register, the Special Refund Entitlement Register and the Register on Reimbursement Drugs. Information from the different registers was merged through record linkages, based on the unique personal identification numbers assigned to all Finnish citizens and permanent residents.

Compilation of register data was conducted with a contract between the three participating governmental organizations and with permissions from the register administrators: the Finnish Medicines Agency, the National Institute for Health and Welfare and the Social Insurance Institution (SII) of Finland. The Institutional Review Board of the National Institute for Health and Welfare and the data protection authority in Finland gave their positive statements for the data collection. The registered people were not contacted and therefore no informed consents were required according to the Finnish regulations.

2.1 Identification of Pregnancies, Background Factors, Possible Confounders and Outcomes

The data consisted of all singleton births in Finland during 1996–2008 ($n = 751{,}139$). Information was obtained from the MBR, maintained by the National Institute for Health and Welfare, and included information on all live births and stillbirths [12, 13] with a gestational age of 22 gestational weeks or more or with a birth weight of 500 g or more. The register includes data on maternal background and medical history, healthcare and medical interventions during pregnancy and delivery, as well as infant outcome up to the age of 7 days. The register does not include information on maternal medications or alcohol use. Register data are collected from all maternity hospitals by the National Institute for Health and Welfare. Data on missing births are supplemented from birth and death certificates. Information on perinatal deaths (stillbirths or deaths during the first week of life) is revised and supplemented from the Cause-of-Death Register, maintained by Statistics Finland. For this study, information on all deaths at the age of 7–365 days was also obtained from the same data source. In cases with conflicting or missing information, the register data were confirmed and supplemented from the maternity hospital records. According to data quality studies, the majority of the register content corresponds well or satisfactorily with hospital record data [13, 14]. Information on MCAs (yes/no) was obtained from the Finnish Malformation Register maintained by the National Institute for Health and Welfare. The register includes information on all births and pregnancy terminations in Finland with at least one detected MCA classified and coded according to the WHO International Classification of Diseases, 9th edition (ICD-9). Minor anomalies are principally excluded from the register according to the European Surveillance of Congenital Anomalies (EUROCAT) [15].

2.2 Information on Maternal Epilepsy and Antiepileptic Drug Purchases

All Finnish citizens and permanent residents in Finland are covered by a national social insurance scheme. Reimbursement of medical purchases is part of a three-level health reimbursement system: SII finances a proportion of drug purchases depending on the refund category; basic refund (currently 42 %, covering all citizens) and two special reimbursement categories (lower 72 %, upper 100 %, granted to persons with a diagnosis of a chronic disease, such as epilepsy, listed in the legislation on drug reimbursements) [16]. Information on entitlement to upper special reimbursement for drug treatment due to maternal epilepsy was obtained from the Special Refund Entitlement Register, maintained by SII. The register includes information on the patient, disease, date of eligibility approval of the reimbursement and type of reimbursement.

Information on maternal AED purchases was obtained from the Register on Reimbursement Drugs maintained by SII. The register collects information on the reimbursed prescription-only drug purchases from all pharmacies in Finland. The register data include information relating to the medicine: the International Anatomic Therapeutic Chemical (ATC) classification code, dose, number of

purchases and the patient's possible special reimbursement status. The Register on Reimbursed Drugs comprises all purchases of medicines directly reimbursed upon purchase at pharmacies (98 % of all reimbursements in 2006) [16]. Over-the-counter drugs or medications given in hospitals or to institutionalized persons are not included in the register.

2.3 Exposure and Outcome Measurement

Entitlement to the upper special reimbursement due to epilepsy was used as an indicator for maternal epilepsy (exposed/unexposed). This was considered valid if at least 1 day of the entitlement period coincided with pregnancy.

Maternal AED purchases under ATC category N03 (antiepileptics) were used as an indicator for AED exposure during pregnancy. AED exposure was defined to include the period of 1 month prior to pregnancy and/or any time during pregnancy (defined by pregnancy trimesters). As drugs are supplied to the patient for a maximum of 3 months at a time, inclusion of purchases occurring during 1 month prior to pregnancy enabled inclusion of women potentially using AEDs in early pregnancy.

2.4 Pregnancy, Perinatal and Infant Health Outcomes

The following pregnancy outcomes were investigated: any CS, elective CS (ECS; performed on a pregnant woman on the basis of an obstetric or medical indication or at the request of the pregnant patient; ECSs are included in CSs), perinatal death (stillbirth, or death during 0–6 days of life), preterm birth (<37 completed gestational weeks), low birth weight (<2,500 g), birth weight adjusted for gestational age: SGA (±2 standard deviation [SD] between 24 and 43 gestational weeks) or large-for-gestational age (LGA ±2 SD between 24 and 43 gestational weeks) according to the sex-specific national standards [17], low Apgar score (<7 at 1 and 5 min), need for respiratory treatment, admission to neonatal care unit (intensive care unit or the neonatal ward) and infant death (0–364 days of age).

2.5 Statistical Analyses

Statistical analyses were performed using SAS® (version 9.1; SAS Institute, Cary, NC, USA) [18] logistic regression modelling (odds ratio [OR] with 95 % confidence intervals). Comparisons were made between offspring of WWE on AED and offspring of reference women with no epilepsy diagnosis and no AED use (WOE). Further analyses were conducted within the cohort of WWE, between AED exposed and AED unexposed in general, and in more detail by type of therapy: monotherapy (one AED type during pregnancy) and polytherapy (more than one AED type during pregnancy) including phenytoin, clonazepam, carbamazepine, oxcarbazepine, valproate, lamotrigine and levetiracetam. For other AEDs, the number of exposed women were too small ($n = 0$–42) to conduct meaningful analyses. Maternal age at delivery, parity, maternal residence divided within five university hospital districts, socioeconomic status (upper white collar, lower white collar, blue collar worker, other, unknown) based on maternal occupation and offspring's MCA (yes/no) were included in the analyses as potential confounding factors.

Inclusion criteria of the study groups varied in the analyses by outcomes: (a) singleton births: CS and ECS, perinatal death; (b) singleton live births: preterm birth, low birth weight, SGA, LGA and infant death; and (c) full-term singleton live births: low Apgar score, need for respiratory treatment and admission to neonatal care unit. In the last group, AED-exposed offspring of WWE included only those with at least third-trimester exposure. Births with AED exposure without maternal epilepsy diagnosis were excluded ($n = 1{,}006$) from the analyses, as this group probably included AED use for other indications than epilepsy, and persons with epileptic symptoms on AED treatment but no confirmed diagnosis.

3 Results

WWE were more likely to smoke during pregnancy and to have previous miscarriages, lower socioeconomic status and other chronic diseases than WOE (Table 1). Of all infants ($n = 751{,}139$), 4,867 (0.6 %) were exposed to maternal epilepsy during pregnancy (Table 1). More than half of the offspring of WWE were exposed to an AED ($n = 3{,}067$, 63.0 %) 1 month prior to and/or during pregnancy. Of these, more than 80 % were exposed to monotherapy. The most commonly used AED was carbamazepine ($n = 1{,}292$, of which 83.9 % was monotherapy) (Table 2).

There was no difference in the median gestational age between the offspring of WWE and WOE (40.0 vs. 40.0), but the mean birth weight was slightly lower in offspring of WWE (3,503 g, SD 588, median 3,525 vs. 3,547 g, SD 544, median 3,565) ($p < 0.0001$). The proportion of stillbirths did not significantly differ between the groups (0.47 vs. 0.34 %, respectively) ($p = 0.11$). Adverse perinatal and infant health outcomes according to maternal epilepsy are shown in Tables 2 and 3.

WWE had a slightly increased risk for CS and ECS compared with WOE (Table 4). Full-term offspring of WWE were at clearly increased risks for need for respiratory treatment and admission to a neonatal care unit compared with offspring of WOE (Table 5).

In relation to WWE with no AED, WWE with AED monotherapy did not have an increased risk of CS or ECS,

Table 1 Maternal background characteristics in singleton pregnancies ending in delivery according to maternal epilepsy and antiepileptic drug (AED) purchases 1 month prior to and/or during pregnancy: Finland, 1996–2008

Characteristic	Women with epilepsy [n (%)]			Women without epilepsy [n (%)]
	Overall	AED	No AED	No AED
Births	4,867 (100.0)	3,067 (100.0)	1,800 (100.0)	721,948 (100.0)
Maternal age at delivery (years)				
Less than 20	168 (3.5)	107 (3.5)	61 (3.4)	20,055 (2.8)
20–34	3,842 (78.9)	2,480 (80.9)	1,362 (75.7)	570,622 (79.0)
35 or more	857 (17.6)	480 (15.7)	377 (20.9)	131,271 (18.2)
Nulliparous	2,029 (41.7)	1,340 (43.7)	689 (38.3)	298,205 (41.3)
Previous miscarriages (≥1)	1,207 (24.8)	757 (24.7)	450 (25.0)	146,843 (20.3)
Any smoking during pregnancy	878 (18.0)	538 (17.5)	340 (18.9)	106,171 (14.7)
Socioeconomic status				
Upper white collar worker	486 (10.0)	295 (9.6)	191 (10.6)	106,336 (14.7)
Lower white collar worker	1,488 (30.6)	908 (29.6)	580 (32.2)	230,522 (31.9)
Blue collar worker	780 (16.0)	485 (15.8)	295 (16.4)	93,476 (12.9)
Other[a]	899 (18.5)	603 (19.7)	296 (16.4)	111,562 (15.5)
Unknown	1,214 (24.9)	776 (25.3)	438 (24.3)	180,052 (24.9)
Number of special reimbursement entitlements				
0				679,219 (94.1)
1	4,492 (92.3)	2,845 (92.8)	1,647 (91.5)	39,961 (5.5)
2	337 (6.9)	201 (6.6)	136 (7.6)	2,538 (0.4)
3 or more	38 (0.8)	21 (0.7)	17 (0.9)	230 (0.0)

[a] Including housewives, students, entrepreneurs/farmers, unemployed, etc

but WWE with AED polytherapy had an increased risk of these outcomes (CS adjusted OR [aOR] 1.47, 95 % CI 1.15–1.87; ECS aOR 1.84, 95 % CI 1.36–2.49) (see Electronic Supplementary Material [ESM] e-table 1). A clearly increased risk of admission to a neonatal care unit was observed in full-term offspring of WWE with AED polytherapy (2.17, 95 % CI 1.56–3.00) compared with full-term offspring of WWE with no AED (see ESM e-table 2).

Offspring of WWE on carbamazepine therapy had a more than twofold increased risk of perinatal mortality and almost threefold increased risk of infant death compared with offspring of WOE (Table 4). Full-term offspring of WWE had a more than twofold increased risk of needing respiratory treatment compared with offspring of WOE (Table 5). Furthermore, a fourfold risk increase for infant death was observed in carbamazepine-exposed offspring compared with offspring of WWE with no AED, even after adjusting for MCA (aOR 4.09, 95 % CI 1.29–12.93) (see ESM e-table 1).

Full-term offspring exposed to valproate had a more than twofold increased risk of a low 5-min Apgar score, respiratory treatment and admission to a neonatal care unit compared with offspring of WOE (Table 5). In addition, a more than twofold risk increase of admission to a neonatal care unit was observed compared with offspring of WWE with no AED after adjusting for MCA (aOR 2.07, 95 % CI 1.60–2.68) (see ESM e-table 2).

WWE receiving oxcarbazepine therapy had an increased risk of CS and ECS compared with WOE (Table 4). Full-term offspring exposed to oxcarbazepine had a clearly increased risk of admission to a neonatal care unit compared with offspring of WOE (Table 5).

WWE on lamotrigine therapy had an increased risk of CS and ECS compared with WOE (Table 4). Full-term offspring exposed to lamotrigine were clearly at an increased risk of admission to a neonatal care unit, both compared with offspring of WOE (Table 5) and WWE with no AED (see ESM e-table 2).

WWE on clonazepam therapy had clearly increased risk for ECS (aOR 2.24, 95 % CI 1.45–3.46) compared with WOE (Table 4). Offspring of WWE exposed to clonazepam had from two- to fourfold increased risks for preterm birth, low birth weight, SGA infant death and admission to a neonatal care unit (Tables 4, 5). In addition, the risk of admission to a neonatal care unit was clearly increased with clonazepam exposure compared with WWE with no AED (see ESM e-table 2). The results were mainly based on cases with polytherapy exposure, as the number of offspring with clonazepam monotherapy exposure was small ($n = 14$).

Table 2 Adverse perinatal and infant health outcomes in singleton pregnancies according to maternal epilepsy and antiepileptic drug exposure 1 month prior to and/or during pregnancy: Finland, 1996–2008

Exposure group (n = births/live births)	CS[a] [n (%)]	Elective CS[a] [n (%)]	Perinatal death[b] [n (1/1,000)]	Preterm birth[c] [n (%)]	Low birth weight[d] [n (%)]	SGA[e] [n (%)]	LGA[e] [n (%)]	Infant death[f] [n (%)]
No maternal epilepsy and no AED exposure(n = 721,948/719,509)	114,791 (15.9)	51,322 (7.1)	3,543 (4.9)	30,027 (4.2)	21,546 (2.0)	14,079 (2.0)	21,574 (3.0)	2,048 (0.3)
Maternal epilepsy(n = 4,867/4,844)	921 (18.9)	463 (9.5)	39 (8.0)	252 (5.2)	207 (4.3)	115 (2.4)	167 (3.4)	27 (0.6)
No AED exposure (n = 1,800/1,793)	331 (18.4)	159 (8.8)	10 (5.6)	85 (4.7)	65 (3.6)	42 (2.3)	71 (4.0)	5 (0.3)
AED exposure (n = 3,067/3,051)	590 (19.2)	304 (9.9)	29 (9.5)	167 (5.5)	142 (4.7)	73 (2.4)	96 (3.1)	22 (0.7)
Monotherapy (n = 2,566/2,551)	455 (17.7)	224 (8.7)	24 (9.4)	135 (5.3)	109 (4.3)	52 (2.0)	87 (3.4)	16 (0.6)
Polytherapy (n = 501/500)	135 (26.9)	80 (16.0)	5 (10.0)	32 (6.4)	33 (6.6)	21 (4.2)	9 (1.8)	6 (1.2)
Phenytoin (n = 53/53)	10 (18.9)	5 (9.4)	0 (–)	4 (7.5)	2 (3.8)	1 (–)	4 (7.5)	0 (–)
Monotherapy (n = 26/26)	1 (3.8)	1 (3.8)	0 (–)	2 (7.7)	1 (3.8)	0 (–)	3 (11.5)	0 (–)
Polytherapy (n = 27/27)	9 (33.3)	4 (14.8)	0 (–)	2 (7.4)	1 (3.7)	1 (3.7)	1 (3.7)	0 (–)
Clonazepam (n = 164/164)	41 (25.0)	24 (14.6)	2 (12.2)	14 (8.5)	13 (7.9)	8 (4.9)	2 (1.2)	3 (1.8)
Monotherapy (n = 14/14)	1 (7.1)	0 (–)	0 (–)	1 (7.1)	2 (14.3)	1 (7.1)	0 (–)	0 (–)
Polytherapy (n = 150/150)	40 (26.7)	24 (16.0)	2 (13.3)	13 (8.7)	11 (7.3)	7 (4.7)	2 (1.3)	3 (2.0)
Carbamazepine (n = 1,292/1,284)	240 (18.6)	127 (9.8)	15 (11.6)	75 (5.8)	67 (5.2)	29 (2.3)	43 (3.3)	12 (0.9)
Monotherapy (n = 1,084/1,077)	191 (17.6)	98 (9.0)	10 (9.2)	58 (5.4)	51 (4.7)	19 (1.8)	39 (3.6)	6 (0.6)
Polytherapy (n = 208/207)	49 (23.6)	29 (13.9)	5 (24.0)	17 (8.2)	16 (7.7)	10 (4.8)	4 (1.9)	6 (2.9)
Oxcarbazepine (n = 695/689)	141 (20.3)	71 (10.2)	8 (11.5)	32 (4.6)	30 (4.4)	27 (3.9)	17 (2.5)	3 (0.4)
Monotherapy (n = 532/527)	99 (18.6)	49 (9.2)	7 (13.2)	23 (4.4)	19 (3.6)	18 (3.4)	15 (2.8)	3 (0.6)
Polytherapy (n = 163/162)	42 (25.8)	22 (13.5)	1 (6.1)	9 (5.6)	11 (6.8)	9 (5.6)	2 (1.2)	0 (–)
Valproate (n = 944/941)	201 (21.3)	112 (11.9)	10 (10.6)	54 (5.7)	43 (4.6)	18 (1.9)	32 (3.4)	9 (1.0)
Monotherapy (n = 706/703)	126 (17.8)	64 (9.1)	7 (9.9)	40 (5.7)	28 (4.0)	12 (1.7)	26 (3.7)	6 (0.9)
Polytherapy (n = 238/238)	75 (31.5)	48 (20.2)	3 (1.3)	14 (5.9)	15 (6.3)	6 (2.5)	6 (2.5)	3 (1.3)
Lamotrigine (n = 345/345)	76 (22.0)	37 (10.7)	0 (–)	15 (4.3)	14 (4.1)	6 (1.7)	3 (0.9)	2 (0.6)
Monotherapy (n = 173/173)	32 (18.5)	11 (6.4)	0 (–)	8 (4.6)	6 (3.5)	2 (1.2)	2 (1.2)	1 (0.6)
Polytherapy (n = 172/172)	44 (25.6)	26 (15.1)	0 (–)	7 (4.1)	8 (4.7)	4 (2.3)	1 (0.6)	1 (0.6)
Levetiracetam (n = 56/56)	17 (30.4)	8 (14.3)	0 (–)	6 (10.7)	6 (10.7)	2 (3.6)	0 (–)	0 (–)
Monotherapy (n = 13/13)	3 (23.1)	0 (–)	0 (–)	2 (15.4)	2 (15.4)	0 (–)	0 (–)	0 (–)
Polytherapy (n = 43/43)	14 (32.6)	8 (18.6)	0 (–)	4 (9.3)	4 (9.3)	2 (4.7)	0 (–)	0 (–)

AED antiepileptic drug, *CS* Caesarean section, *LGA* large for gestational age, *SGA* small for gestational age

[a] Including live births and stillbirths, total n = 751,139

[b] Stillbirth or early neonatal death (0–6 days of age)

[c] <37 gestational weeks

[d] <2,500 g

[e] According to the sex-specific national standards

[f] Death during the first year of life (0–364 days of age)

Table 3 Respiratory treatment, admission to neonatal care unit, and low Apgar score in singleton pregnancies ending in full-term (≥37 gestational weeks) live birth according to maternal epilepsy and antiepileptic drug (AED) exposure during pregnancy, or the third trimester of pregnancy: Finland, 1996–2008

Exposure group	Total number of births 1996–2008 (n)	Respiratory treatment [n (%)]	Admission to neonatal care unit [n (%)]	1-min Apgar <7 [n (%)]	Total number of births 2004–2008 (n)	5-min Apgar <7[a] [n (%)]
No maternal epilepsy and no AED exposure	689,482	2,962 (0.4)	49,612 (7.2)	27,939 (4.1)	269,151	3,014 (1.1)
Maternal epilepsy	4,592	48 (1.0)	545 (11.9)	227 (4.9)	1,808	15 (0.8)
No AED exposure during pregnancy	1,708	12 (0.7)	152 (8.9)	69 (4.0)	652	3 (0.5)
AED exposure during the third trimester	2,541	32 (1.3)	346 (13.6)	143 (5.6)	1,017	11 (1.1)
Monotherapy	2,184	28 (1.3)	275 (12.6)	120 (5.5)	877	9 (1.0)
Polytherapy	357	4 (1.1)	71 (19.9)	23 (6.4)	140	2 (1.4)
Phenytoin	41	1 (2.4)	3 (7.3)	1 (2.4)	5	1 (20.0)
Monotherapy	21	0 (–)	0 (–)	0 (–)	2	0 (–)
Polytherapy	20	1 (5.0)	3 (15.0)	1 (5.0)	3	1 (33.3)
Clonazepam	114	2 (1.8)	25 (21.9)	9 (7.9)	38	1 (2.6)
Monotherapy	12	1 (8.3)	3 (25.0)	2 (16.7)	5	1 (20.0)
Polytherapy	102	1 (1.0)	22 (21.6)	7 (6.9)	33	0 (–)
Carbamazepine	1,038	11 (1.1)	111 (10.7)	44 (4.2)	277	3 (1.1)
Monotherapy	904	10 (1.1)	89 (9.8)	36 (4.0)	248	2 (0.8)
Polytherapy	134	1 (0.7)	22 (16.4)	8 (6.0)	29	1 (3.4)
Oxcarbazepine	573	5 (0.9)	69 (12.0)	32 (5.6)	282	2 (0.7)
Monotherapy	465	3 (0.6)	46 (9.9)	27 (5.8)	230	2 (0.9)
Polytherapy	108	2 (1.9)	23 (21.3)	5 (4.6)	52	0 (–)
Valproate	771	14 (1.8)	147 (19.1)	62 (8.0	290	9 (3.1)
Monotherapy	600	12 (2.0)	110 (18.3)	45 (7.5)	235	7 (3.0)
Polytherapy	171	2 (1.2)	37 (21.6)	17 (9.9)	55	2 (3.6)
Lamotrigine	289	3 (1.0)	52 (18.0)	14 (4.8)	207	4 (1.9)
Monotherapy	154	2 (1.3)	24 (15.6)	9 (5.8)	132	3 (2.3)
Polytherapy	135	1 (0.7)	28 (20.7)	5 (3.7)	75	1 (1.3)
Levetiracetam	40	0 (–)	6 (15.0)	2 (5.0)	39	0 (–)
Monotherapy	12	0 (–)	2 (16.7)	1 (8.3)	12	0 (–)
Polytherapy	28	0 (–)	4 (14.3)	1 (3.6)	27	0 (–)

[a] Information available for years 2004–2008

WWE on levetiracetam therapy had a more than twofold increased risk of CS and ECS (Table 4), and their offspring had a more than twofold increased risk of preterm birth and more than threefold increased risk of low birth weight compared with offspring of WOE (Table 4). The number of levetiracetam exposures was low ($n = 56$), especially monotherapy ($n = 13$).

4 Discussion

The aim of this study was to evaluate the effect of maternal epilepsy and related AED use on perinatal health outcomes in offspring. This study was based on a large population-based cohort of singleton births including information on more than 4,000 offspring of WWE and more than 2,500 offspring of WWE taking an AED 1 month prior to and/or during pregnancy. Two reference groups were used in this study: WOE and WWE with no AED. Due to the large study population, we were able to conduct detailed analyses based on several individual AEDs.

Overall, we found several increased perinatal health risks in offspring of WWE compared with the reference cohort of WOE. WWE with no AED had only a marginally elevated risk for CS, and their offspring had only a slight risk increase of being admitted to a neonatal care unit compared with the reference group of WOE and their offspring.

Table 4 The risk of Caesarean section, perinatal death, preterm birth, low birth weight, weight for gestational age and infant death according to maternal epilepsy and antiepileptic drug (AED) exposure 1 month prior to pregnancy and/or during pregnancy: singleton pregnancies, Finland, 1996–2006

Exposure group	Births			Live births				
	CS	ECS	Perinatal death[a]	Preterm birth[b]	Low birthweight[c]	SGA[d]	LGA[d]	Infant death[e]
Epilepsy, overall	1.24 (1.15–1.34)*	1.39 (1.26–1.53)*	1.40 (1.01–1.93)*	1.20 (1.05–1.36)*	1.34 (1.16–1.54)*	1.14 (0.94–1.37)	1.14 (0.98–1.34)	1.47 (0.99–2.18)
No AED	1.20 (1.07–1.36)*	1.25 (1.06–1.47)*	0.99 (0.51–1.92)	1.12 (0.90–1.40)	1.19 (0.92–1.53)	1.19 (0.88–1.63)	1.29 (1.01–1.63)*	0.72 (0.27–1.94)
AED	1.27 (1.16–1.39)*	1.48 (1.32–1.67)*	1.60 (1.10–2.32)*	1.24 (1.06–1.45)*	1.42 (1.20–1.69)*	1.10 (0.87–1.39)	1.06 (0.86–1.30)	1.81 (1.18–2.79)*
Monotherapy	1.15 (1.04–1.28)*	1.29 (1.13–1.49)*	1.69 (1.12–2.54)*	1.22 (1.03–1.45)*	1.35 (1.11–1.64)*	0.96 (0.73–1.27)	1.15 (0.93–1.43)	1.74 (1.05–2.88)*
Polytherapy	1.89 (1.54–2.31)*	2.52 (1.98–3.20)*	1.27 (0.52–3.09)	1.33 (0.93–1.91)	1.76 (1.22–2.53)*	1.73 (1.11–2.70)*	0.59 (0.30–1.14)	2.02 (0.88–4.64)
Phenytoin	1.18 (0.59–2.36)	1.21 (0.48–3.06)		1.62 (0.58–4.53)	1.04 (0.25–4.32)	0.79 (0.11–5.82)	2.29 (0.82–6.35)	
Monotherapy	0.22 (0.03–1.64)	0.45 (0.06–3.33)		1.85 (0.43–7.88)	1.33 (0.18–9.92)		3.23 (0.96–10.83)	
Polytherapy	2.36 (1.04–5.35)*	2.10 (0.72–6.10)		1.43 (0.33–6.15)	0.84 (0.11–6.35)	1.26 (0.17–9.57)	1.21 (0.16–8.96)	
Clonazepam	1.77 (1.24–2.53)*	2.24 (1.45–3.46)*	1.73 (0.42–7.08)	1.95 (1.12–3.39)*	2.41 (1.36–4.29)*	2.20 (1.07–4.51)*	0.38 (0.10–1.54)	3.70 (1.12–12.3)*
Monotherapy	0.43 (0.06–3.27)			1.95 (0.25–14.95)	6.14 (1.36–27.72)*	4.22 (0.55–32.66)		
Polytherapy	1.93 (1.33–2.78)*	2.49 (1.60–3.86)*	1.81 (0.44–7.45)	1.95 (1.10–3.46)	2.16 (1.16–4.03)*	2.06 (0.96–4.42)	0.42 (0.10–1.69)	3.82 (1.15–12.7)
Carbamazepine	1.22 (1.05–1.40)*	1.39 (1.16–1.67)*	2.23 (1.33–3.73)*	1.40 (1.11–1.77)*	1.71 (1.33–2.20)*	1.13 (0.78–1.63)	1.06 (0.78–1.44)	2.86 (1.60–5.14)*
Monotherapy	1.16 (0.99–1.36)	1.27 (1.03–1.57)*	1.92 (1.02–3.60)*	1.32 (1.01–1.72)*	1.63 (1.23–2.17)*	0.91 (0.58–1.44)	1.15 (0.83–1.58)	1.94 (0.86–4.39)
Polytherapy	1.51 (1.09–2.09)*	2.02 (1.36–2.99)*	3.27 (1.32–8.14)*	1.79 (1.09–2.96)*	2.07 (1.21–3.54)*	2.08 (1.09–3.97)*	0.60 (0.22–1.62)	5.62 (2.35–13.4)*
Oxcarbazepine	1.35 (1.11–1.62)*	1.60 (1.25–2.05)*	2.00 (0.98–4.05)	1.04 (0.73–1.48)	1.33 (0.92–1.93)	1.82 (1.23–2.68)	0.88 (0.54–1.43)	1.11 (0.35–3.51)
Monotherapy	1.21 (0.97–1.51)	1.43 (1.06–1.92)*	2.55 (1.20–5.44)	1.00 (0.66–1.52)	1.14 (0.72–1.81)	1.64 (1.02–2.64)*	1.03 (0.61–1.72)	1.74 (0.55–5.55)
Polytherapy	1.83 (1.28–2.61)*	2.19 (1.40–3.45)*	0.79 (0.11–5.69)	1.15 (0.58–2.25)	1.88 (1.01–3.51)*	2.34 (1.18–4.62)*	0.43 (0.11–1.72)	
Valproate	1.43 (1.22–1.68)*	1.87 (1.54–2.29)*	1.45 (0.77–2.73)	1.21 (0.92–1.60)	1.23 (0.90–1.69)	0.79 (0.49–1.26)	1.17 (0.82–1.67)	1.70 (0.87–3.34)
Monotherapy	1.16 (0.96–1.42)	1.41 (1.09–1.82)*	1.49 (0.70–3.18)	1.24 (0.90–1.71)	1.14 (0.78–1.67)	0.72 (0.41–1.29)	1.30 (0.88–1.93)*	1.76 (0.77–4.01)
Polytherapy	2.36 (1.79–3.13)*	3.39 (2.46–4.66)*	1.35 (0.43–4.28)	1.15 (0.67–1.99)	1.49 (0.86–2.58)	0.95 (0.42–2.14)	0.82 (0.36–1.85)	1.60 (0.50–5.12)
Lamotrigine	1.50 (1.15–1.94)*	1.71 (1.21–2.41)*		0.90 (0.54–1.52)	1.12 (0.65–1.93)	0.72 (0.32–1.61)	0.31 (0.10–0.95)	1.21 (0.30–4.97)
Monotherapy	1.20 (0.81–1.77)	0.99 (0.53–1.82)		0.98 (0.48–2.00)	0.99 (0.43–2.25)	0.49 (0.12–1.97)	0.42 (0.10–1.68)	1.41 (0.19–10.37)
Polytherapy	1.82 (1.29–2.58)*	2.49 (1.63–3.79)*		0.83 (0.39–1.77)	1.26 (0.61–2.58)	0.93 (0.34–2.53)	0.20 (0.03–1.40)	1.06(0.14–7.79)
Levetiracetam	2.33 (1.30–4.16)*	2.52 (1.19–5.39)*		2.54 (1.08–5.97)*	3.47 (1.46–8.23)*	1.58 (0.38–6.56)		
Monotherapy	1.49 (0.41–5.48)			3.54 (0.77–16.36)	4.74 (1.01–22.18)*			
Polytherapy	2.64 (1.38–5.07)*	3.35 (1.55–7.27)*		2.23 (0.79–6.29)	3.07 (1.08–8.74)*	2.20 (0.52–9.25)		

All data are presented as aOR (95 % CI). Women without epilepsy and AED use and their offspring were used as a reference group

Blank cells indicate no results due to small numbers or zero observations

aOR odds ratio adjusted for maternal age at delivery, parity, university hospital district, socioeconomic status and major congenital anomalies, *CS* Caesarean section, *ECS* elective Caesarean section, *LGA* large for gestational age, *SGA* small for gestational age

* Significant findings

[a] Stillbirth or early neonatal death (0–6 days of age)

[b] <37 completed gestational weeks

[c] <2,500 g

[d] According to sex-specific national standards (± 2 SD)

[e] Death during the first year of life (0–364 days of age)

Our results support those of previous studies that have observed higher obstetric and perinatal risks among WWE on AED [3, 4, 8, 9, 19]. In our study, the risks of several adverse outcomes were clearly elevated: a two- to threefold increase with polytherapy. However, a more than twofold increased risk of needing respiratory treatment was also observed for offspring of WWE with AED monotherapy compared with offspring of WOE. Effects of epilepsy and AEDs, or different types of epilepsy, could not be distinguished, making confounding by indication possible in this study.

Some previous studies have found an elevated risk for CS or ECS in WWE [2, 7, 10, 20]. However, we found only a slightly elevated risk for CS and ECS in WWE compared with WOE. WWE with frequent seizures are at high risk for seizures during labour, and are therefore likely to have a planned CS [5]. The majority of WWE had vaginal delivery (81.1 % vs. WOE 83.5 %) in our study.

Two previous studies [9, 20] have reported an increased risk of preterm birth in offspring of WWE. The overall risk for preterm birth was only slightly increased in our study. In terms of AEDs, our results also support the previous findings of an association between preterm birth and carbamazepine exposure [19]. Some studies have suggested that the risk for preterm birth is especially increased in offspring of WWE who are smokers [3, 21], and therefore we conducted separate analyses on preterm birth between WWE and WOE by maternal smoking. We did not find any differences in risk for preterm birth between these groups (results not shown). We did not include smoking in the analyses, as it has been found to correlate strongly with socioeconomic status in Finland [22]. Socioeconomic status was used as a potential confounding factor in our study.

We found an increased risk of low birth weight in offspring overall exposed to AEDs, or to carbamazepine, clonazepam or levetiracetam. These findings are partly in line with previous studies, which observed an increased risk of low birth weight in offspring of WWE on AEDs [3, 4, 20], including lamotrigine, carbamazepine or AED polytherapy. Only a few studies have assessed the risk of maternal clonazepam or levetiracetam exposure and low birth weight [23, 24]. We found an almost 2.5-fold risk increase of low birth weight in offspring exposed to clonazepam compared with offspring of WOE, and an approximately sixfold risk increase in offspring exposed to clonazepam monotherapy compared with offspring of WOE or WWE with no AED. However, there were only 164 infants exposed to clonazepam in our data (monotherapy, $n = 14$) and, accordingly, the results are based on a small number of newborns.

The overall risk for perinatal death was only marginally elevated, and infant mortality was not increased in offspring of WWE compared with offspring of WOE in this study. Some previous studies have found a slightly increased risk of perinatal mortality in offspring of WWE [25, 26], whereas other studies have not [2, 4, 5, 8]. Few studies have conducted more detailed analyses on different AEDs and the risk of perinatal or infant mortality. We found a more than twofold increased risk of perinatal death in offspring exposed to maternal carbamazepine compared with offspring of WOE. Furthermore, the risk of infant death was from three- to fourfold higher among offspring exposed to clonazepam or carbamazepine than in offspring of WOE, even after adjusting for MCA.

We observed an increased risk of low 1- and 5-min Apgar scores in full-term infants of WWE. Valproate exposure was related to an almost twofold higher risk of a low 1-min Apgar score and an almost threefold higher risk of a low 5-min Apgar score. Some previous studies have observed an increased risk of low 5-min Apgar scores among maternal AED-exposed offspring [10, 19, 20]. Information on 5-min Apgar scores was not available in the MBR until 2004, and our results are therefore based on data from 5 years only.

In our study, full-term offspring of WWE on AED therapy were at an increased risk of needing respiratory treatment compared with offspring of WOE, which is in line with a previous finding suggesting that the risk of respiratory distress is clearly increased in offspring of WWE [7]. We found a more than threefold increased risk in maternal valproate monotherapy-exposed offspring compared with offspring of WOE. This finding supports the previously reported association between maternal valproate exposure during pregnancy and neonatal respiratory complications [27–29].

We observed an increased risk of being admitted to a neonatal care unit in offspring of WWE compared with offspring of WOE. This risk was increased regardless of type of AED exposure. The highest risks of admission to a neonatal care unit were seen in offspring of WWE exposed to clonazepam, valproate or lamotrigine. Our results are in line with a previous study that observed a nearly twofold risk for admission to neonatal care units in offspring of WWE, including clearly elevated risks associated with exposure to maternal clonazepam, valproate or lamotrigine [20].

Our data are nation-wide, based on compulsory administrative health registers with high quality and coverage. The MBR covers 99 % of all births in Finland and the validity of the register is good, and the Drug Reimbursement Register covers 98 % of all drug reimbursements. These national registers offer a valuable database for research purposes to investigate drug-induced fetal adverse effects. A rigorous description of the registers and their use in research has been given recently in the literature [1]. The register-based setting offers several advantages as selection

Table 5 Comparison of the risk of a low Apgar score, needing respiratory care or care at observation unit in newborn offspring of epilepsy patients by maternal epilepsy and antiepileptic drug (AED) exposure compared with a reference cohort without epilepsy and AED therapy during the third trimester of pregnancy: full-term offspring of singleton live births, Finland, 1996–2008

Exposure group[a]	Respiratory care	Care at observation unit	1-min Apgar <7	5-min Apgar[b] <7
Epilepsy, overall	2.10 (1.57–2.81)*	1.65 (1.51–1.81)*	1.19 (1.04–1.36)*	1.30 (0.89–1.91)
No AED	1.60 (0.90–2.83)	1.25 (1.06–1.49)*	1.01 (0.79–1.28)	1.06 (0.53–2.14)
AED	2.35 (1.65–3.36)*	1.89 (1.68–2.12)*	1.33 (1.12–1.57)*	1.53 (0.96–2.45)
Monotherapy	2.57 (1.76–3.76)*	1.76 (1.55–2.00)*	1.32 (1.09–1.59)*	1.51 (0.91–2.53)
Polytherapy	1.46 (0.54–3.96)	2.70 (2.06–3.54)*	1.37 (0.89–1.12)	1.61 (0.51–5.11)
Phenytoin	3.35 (0.43–25.91)	0.81 (0.25–2.68)	0.57 (0.08–4.20)	23.42 (2.57–213.1)*
Monotherapy				
Polytherapy	5.44 (0.65–45.44)	1.65 (0.47–5.86)	1.07 (0.14–8.08)	1.78 (1.40–2.26)*
Clonazepam	2.59 (0.62–10.78)	3.39 (2.14–5.37)*	1.91 (0.96–3.79)	2.51 (0.34–18.82)
Monotherapy	19.10 (2.34–156.2)*	4.52 (1.17–17.47)*	4.75 (1.03–21.98)*	24.51 (2.49–241.2)*
Polytherapy	1.37 (0.19–10.03)	3.28 (2.01–5.34)*	1.63 (0.75–3.53)	
Carbamazepine	2.33 (1.27–4.25)*	1.55 (1.27–1.89)*	1.06 (0.78–1.44)	1.13 (0.36–3.54)
Monotherapy	2.66 (1.42–5.00)*	1.44 (1.16–1.80)*	1.04 (0.74–1.45)	0.85 (0.21–3.42)
Polytherapy	1.01 (0.14–7.34)	2.24 (1.40–3.60)*	1.22 (0.57–2.62)	3.42 (0.46–25.58)
Oxcarbazepine	1.68 (0.69–4.09)	1.62 (1.25–2.09)*	1.27 (0.89–1.82)	0.56 (0.14–2.28)
Monotherapy	1.33 (0.42–4.20)	1.33 (0.98–1.82)	1.33 (0.90–1.97)	0.72 (0.18–2.91)
Polytherapy	2.75 (0.66–11.48)	2.92 (1.80–4.72)*	1.01 (0.41–2.48)	
Valproate	2.71 (1.58–4.66)*	2.64 (2.19–3.18)*	1.84 (1.41–2.40)*	2.70 (1.38–5.24)*
Monotherapy	3.38 (1.88–6.07)*	2.59 (2.09–3.21)*	1.76 (1.29–2.39)*	2.72 (1.28–5.81)*
Polytherapy	1.23 (0.30–5.04)	2.79 (1.90–4.10)*	2.12 (1.26–3.58)*	2.62 (0.63–10.94)
Lamotrigine	1.48 (0.47–4.67)	2.40 (1.76–3.27)*	0.97 (0.56–1.66)	1.37 (0.51–3.70)
Monotherapy	1.94 (0.47–8.02)	1.97 (1.26–3.08)*	1.15 (0.59–2.27)	1.69 (0.53–5.36)
Polytherapy	1.00 (0.14–7.27)	2.94 (1.91–4.53)*	0.75 (0.30–1.84)	0.87 (0.12–6.30)
Levetiracetam		1.78 (0.73–4.36)	0.95 (0.23–3.96)	
Monotherapy		2.37 (0.52–10.92)	1.69 (0.22–13.21)	
Polytherapy		1.57 (0.52–4.70)	0.66 (0.09–4.87)	

All data are presented as aOR (95 % CI). Women without epilepsy and AED use and their offspring were used as a reference group

Blank cells indicate no results due to small numbers or zero observations

aOR odds ratio adjusted for maternal age at delivery, parity, university hospital district, socioeconomic status and major congenital anomaly

* Significant findings

[a] According to antiepileptic drug exposure during the third trimester of pregnancy

[b] Data available from 2004 onwards

bias is not a concern because the data is derived from the population and there is no loss to follow-up of study subjects. However, a large reference group enables detection of relatively small but statistically significant differences without clear clinical importance. Therefore, the results with a small risk increase should be interpreted with caution. Furthermore, as a large number of comparisons were conducted in our analysis, it may be possible that some of the observed associations may be due to chance.

Our results are mainly comparable with register-based studies conducted in other Nordic countries. Nordic countries each have a partly similar social security system, including reimbursement for drug purchases as well as similarities in drug prescribing patterns and health registers. However, the results of this study may not be applicable to all other countries.

All of the required data, such as maternal alcohol use, is not always available in the routinely collected national health registers. Additionally, information on persons who have refused the full reimbursement for AEDs is not available in the SII database. Furthermore, only persons residing in Finland are entitled to the special reimbursement. We did not have information on emigrants and recent immigrants giving birth in Finland. The number of parturients in these groups, however, is negligible.

Information on purchases of prescribed medicines was used as a proxy for AED use, as we did not have information on actual AED use. According to a previous Danish

study, compliance in the use of prescribed drugs in chronic diseases during pregnancy is high (100 % for epilepsy) [30]. Some WWE may, however, stop using AEDs because of potential risks for the fetus [31, 32], although they may have purchased the prescribed AEDs. This may have affected misclassification bias in this study, resulting in a decrease in the strength of the association between the AED exposure and the study outcomes. However, a previous study of the Finnish registers observed that AEDs were purchased similarly during each trimester as before pregnancy, suggesting that compliance is not a major confounder [33].

Women with epilepsy, especially those with severe disease, may have more intensive follow-up during pregnancy and delivery with more detailed recording, reporting and registration of adverse pregnancy and perinatal outcomes. This may affect the prevalence of adverse perinatal outcomes in the offspring of patients with epilepsy and may have led to overestimation of the perinatal health risks in the offspring of WWE compared with offspring of WOE.

Patients with epilepsy consist of people with different types of epilepsies and severities. Individual pharmacokinetics may vary and, therefore, there may be clear differences in dose effects between the epilepsy patients. Furthermore, the effect of AEDs and epilepsy is even more difficult to distinguish as we did not have information on type of epilepsy or drug dose and, therefore, confounding by indication is possible. It would be important to include type of epilepsy and drug dose in the future studies.

This study was large enough to evaluate the effects of maternal epilepsy and AED use during pregnancy on perinatal health outcomes in newborns. A future study on women with AED use but without epilepsy would provide important information on the relationship between maternal epilepsy, AED use during pregnancy without epilepsy, and perinatal health of their offspring.

5 Conclusions

Offspring of WWE are at an increased risk of neonatal respiratory treatment and admission to a neonatal care unit. The risks are likely to be increased with polytherapy, and confounding by indication may bias the results. Information on type of epilepsy was not included in this study, which may reduce the generalization of our results. In future studies, it is important to include analyses on pregnant women without epilepsy, but who are exposed to AEDs.

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Conflict of interest The authors declare no conflict of interest.

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