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Brief Communication

# Perinatal outcome and healthcare resource utilization in the first year of life after antiepileptic exposure during pregnancy

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ABSTRACT

Healthcare administrative databases of Italy's Lombardy Region were analyzed with the aim to assess perinatal outcomes and healthcare resource utilization during the first year of life in infants exposed to antiepileptic drugs (AEDs) during pregnancy.
Drug prescriptions dispensed in the 12 months before delivery to women, who delivered between 2005 and 2011, were analyzed. Neonates were classified as cases if exposed to AEDs, and each case was randomly matched to seven controls. No significant differences were observed in the risk of congenital malformations between 526 cases and 3682 controls except for valproic acid (odds ratio (OR): 2.29; 95% confidence interval (CI): 1.24–4.22) where cases were more likely to be small for gestational age ($\chi^2 = 7.66$; $p = 0.006$). Cases also had a higher probability than controls of needing at least one specialist visit in a child neuropsychiatry outpatient service (OR: 1.74; 95% CI: 1.22–2.49).


## 1. Introduction

Epilepsy is the most common chronic neurological disorder with a prevalence between 4 and 10 per 1000 people [1]. The prevalence of epilepsy in pregnant women has been estimated at 0.3–0.7%, and it can complicate pregnancy and perinatal outcomes [2,3].

A slightly higher risk of being small for gestational age (SGA) or low birth weight has been reported in babies prenatally exposed to antiepileptic drugs (AEDs) [4,5]. A population study found that preterm deliveries were more common in women using AEDs, but only for women taking AEDs for indications other than epilepsy [4].

The reported incidence of congenital malformations in the offspring of women with epilepsy taking AEDs can range from 0.6 to 26.1% compared with 2–4% in the general population [6]. A systematic review performed by the Cochrane Collaboration reported that the risk of malformation is significantly higher with valproic acid, carbamazepine, phenytoin, and phenobarbital than with lamotrigine and levetiracetam [5] although the risk is the greatest with valproic acid [7,8]. Prenatal exposure to valproic acid has also been associated with impaired neurodevelopmental growth, including lower intelligence quotient (IQ) and language deficits and a higher risk of developing autism spectrum disorders and attention-deficit hyperactivity disorder (ADHD) [9]. As a result of these findings, international regulatory agencies warned healthcare professionals that valproic acid should not be prescribed to pregnant women or women who can become pregnant unless other treatments are ineffective or not tolerated [10]. Despite some limitations (e.g., variable accuracy of timing the start of pregnancy; data on pregnancies ending in induced abortions are often not available), large mother–newborn cohorts with demographic and clinical information can be built up, and the record linkage between databases is essential to gather the necessary information [11]. In Italy, few studies have used administrative databases to examine the outcome of drug use and have mainly focused on birth outcomes [12]. Therefore, we made an exploratory study using healthcare administrative databases to evaluate birth outcomes after exposure to AED during pregnancy and healthcare resource utilization during the first year of life for Italian children.

## 2. Methods

### 2.1. Data source

The data sources used were four administrative health databases of Italy's Lombardy Region [12], routinely used for reimbursement reasons:

- a database collecting demographic information;
- a prescription database collecting drugs reimbursed by the Italian National Health Service, diagnostic tests, and outpatient specialist visits;

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- hospital discharge forms; and
- birth certificates.

To protect the patient's privacy, all data were anonymized at regional level by the data owner, in accordance with the Italian legislation.

No ethics committee approval is required in Italy for epidemiological studies using healthcare administrative databases for research purposes and with individuals identified by an anonymous patient code.

### 2.2. Drugs

Antiepileptic and psychotropic drugs were classified as belonging respectively to the N03A, N05, and N06 subgroups of the Anatomical Therapeutic Chemical (ATC) classification system [13]. The following drugs were considered teratogens: antineoplastic agents (ATC: L01); retinoids for systemic treatment of acne and psoriasis (ATC: D10BA, D10AD, D05BB); thalidomide; methotrexate (ATC: L04AX02, L04AX03); warfarin (B01AA03); and lithium (ATC: N05AN01). Antiepileptic drug consumption during the 12 months before delivery was measured using the defined daily dose (DDD) [12].

### 2.3. Sample definition

Pregnant women living in 7 of 15 local health units in the Lombardy Region, who delivered between 2005 and 2011, were identified through the hospital discharge form database (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM codes in the diagnosis record: from 650 to 659—normal delivery and other indications for care in pregnancy, labor, and delivery). Based on prescriptions received during the 12 months before delivery, pregnant women were grouped as having the following:

- antiepileptic treatment (receiving >1 prescription of AEDs) and
- other pharmacological treatment (receiving ≥1 drug prescription excluding AEDs and teratogens).

Newborns from mothers in the first group were classified as cases (exposed to AEDs) and newborns from mothers in the second group as controls.

Since one subject can be registered with the National Health Service and receive care from private physicians in Italy, controls were chosen among mothers with drug prescriptions (with the exclusion of teratogens and AEDs) in order to be confident that they can be monitored using public healthcare administrative databases.

Antiepileptic drug exposure during the first trimester of pregnancy was stratified into two groups according to the pregnancy period: the whole pregnancy in one group and before pregnancy and the first trimester in the other group. Cases exposed to AEDs in the second and third trimesters only were excluded from the analyses in view of the absence of malformation risk induction during these periods. The exposure period was estimated starting from the previous 12 months before delivery up to the date of birth.

Neonates were defined as having been exposed to AED monotherapy if their mothers had filled prescriptions for only one antiepileptic active substance or exposed to polytherapy if their mothers had received prescriptions for different antiepileptic active substances. Concomitant therapy with psychotropic drugs was also recorded.

### 2.4. Outcomes

At birth, we recorded the following: gestational age, birth weight for gestational age, Apgar score at 5 min, length of hospital stay (≥6 days), and admission to an intensive care unit. Congenital malformations were gathered from birth certificates and/or hospital admission of the newborn in the first year of life with ICD-9-CM codes from 740 to 760 and 658.8 as the diagnosis on the hospital discharge form [12]. Hospitalization for any causes, prescriptions for diagnostic tests and drugs, and specialist visits in child and adolescent mental health outpatient services for cases and controls were analyzed in the first year of life.

### 2.5. Statistical analysis

For each case, seven neonates not exposed to AEDs were randomly selected and matched for maternal age at birth, type (single/twin), mode (natural/cesarean) of delivery, and number of previous births (primiparous: yes/no).

The 1:7 ratio was calculated to detect a risk ratio ≥2 in exposed versus unexposed subjects, assuming an expected incidence of malformations of 3% in the unexposed group, power more than 0.80, alpha of 0.05, and at least 300 neonates exposed to AEDs. Each control maintained the same exposure period and the monotherapy/polytherapy pattern of the matched case. To identify risk factors associated with exposure to AEDs, univariate and bivariate analyses were done using odds ratios with a 95% confidence interval (CI) and a Mantel–Haenszel chi-squared test for stratified data.

## 3. Results

In all, 526 newborns were identified as cases exposed to AEDs during pregnancy and matched to 3682 controls. A total of 154 newborns were exposed to carbamazepine, 131 to valproic acid, 63 to pregabalin, and 56 to lamotrigine. No significant differences were observed in the risk of congenital malformations between cases and controls except for valproic acid (Table 1). In the latter case, newborns with malformations were exposed to more DDDs of valproic acid than those without malformations (median [interquartile range]: 160 [61–321] vs 93.7 [42–160]; $p = 0.025$). Children exposed to valproic acid were more likely to be SGA (Table 1; $\chi^2 = 7.66$; $p = 0.006$).

Cases exposed to all AEDs were more likely to have had at least one specialist visit in child neuropsychiatry services than controls (Table 2). The likelihood of being visited by a child psychiatrist was markedly higher for children exposed to valproic acid (Table 2).

## 4. Discussion

To the best of our knowledge, this is the first study in Italy that has evaluated health resource utilization in newborns exposed to AEDs. In contrast to a previous Italian study that used healthcare administrative databases [12] to monitor pregnancy outcomes, we found an increased risk of malformations, though the differences were statistically significant only for valproic acid. Moreover, the risk of malformations was found greater in neonates exposed to AED polytherapy, although raw numbers were too small to detect significant differences.

These findings confirm that valproic acid involves the greatest risk of malformations, with an incidence of 11.5% rising to 19% when the drug was taken with other AEDs. The data do not allow any firm conclusion, but we found that valproic acid dose (as DDD) was larger in neonates with malformations than in neonates without malformations. It is therefore likely that the risk of malformations may be at least partly related to the dose [6].

The use of administrative databases as a study data source has provided a picture of current clinical practice but with limitations due to the lack of clinical information, genetic family history, and details concerning lifestyle habits.

Since the main aim of the study was to estimate the risk of malformations and healthcare resource use during the first year of life, we matched cases and controls for the type of delivery. In this regard, our study was not designed to detect differences in birth outcome (i.e., risk of prematurity, SGA), but despite this limitation, we did see a higher risk of being SGA particularly in the group exposed to valproic acid. This finding is also consistent with previous studies [5,14].

**Table 1**
Outcome at birth: cases exposed to all AEDs and to valproic acid only vs controls.

| Outcome at birth | All AEDs | | | Valproic acid | | |
|---|---|---|---|---|---|---|
| | Cases N = 526 | Controls N = 3682 | OR [95% CI] | Cases N = 131 | Controls N = 917 | OR [95% CI] |
| Preterm birth (<37 weeks) | 47 (8.9%) | 246 (6.7%) | 1.37 [0.99–1.90] | 8 (6.1%) | 48 (5.2%) | 1.18 [0.54–2.55] |
| Apgar score at 5 min | | | | | | |
| 0–3 | – | 4 | 0.61 [0.14–2.58] | – | – | 1.17 [0.20–9.78] |
| 4–6 | 2 (0.38%) | 23 (0.62%) | | 1 (0.76%) | 6 (0.65%) | |
| ≥7 | 524 (99.62%) | 3659 (99.38%) | | 130 (99.24%) | 911 (99.35%) | |
| Weight for gestational age | | | | | | |
| Small for gestational age (SGA) | 67 (12.7%) | 350 (9.5%) | $\chi^2 = 3.28$; p = 0.07 | 22 (16.79%) | 75 (8.18%) | $\chi^2 = 7.66$; p = 0.006 |
| Appropriate for gestational age (AGA) | 408 (77.6%) | 2959 (80.4%) | | 97 (74.05%) | 733 (79.93%) | |
| Large for gestational age (LGA) | 51 (9.7%) | 373 (10.1%) | | 12 (9.16%) | 109 (11.89%) | |
| Hospital stay (≥6 days) | 29 (5.5%) | 161 (4.4%) | 1.27 [0.85–1.92] | 9 (6.87%) | 45 (4.91%) | 1.43 [0.68–3.00] |
| ICU stay | – | 3 | – | – | 2 (0.22%) | – |
| Congenital malformations | 37 (7.0) | 188 (5.1) | 1.41 [0.98–2.03] | 15 (11.45%) | 49 (5.34%) | 2.29 [1.24–4.22] |
| Exposure period to drugs | | | | | | |
| Whole pregnancy | 25/307 (8.1)[b] | 121/2149 (5.6)[b] | 1.49 [0.95–2.33] | 12/79 (15.2)[b] | 33/553 (6.0)[b] | 2.82 [1.39–5.73] |
| Before pregnancy and I trimester[a] | 12/219 (5.5)[b] | 67/1533 (4.4)[b] | 1.27 [0.67–2.38] | 3/52 (5.8)[b] | 16/364 (4.4)[b] | 1.33 [0.37–4.74] |
| Polytherapy | 6/47 (11.7)[b] | 18/329 (5.5)[b] | 2.54 [0.95–6.76] | 3/16 (18.8)[b] | 6/112 (5.4)[b] | 3.69 [0.82–16.58] |
| Concomitant therapy with psychotropic drugs | 5/73 (6.8)[b] | 5/57 (8.8)[b] | 0.76 [0.21–2.78] | 2/23 (8.7)[b] | 2/25 (8.0)[b] | 1.10 [0.14–8.49] |

[a] Antiepileptic drug therapy was stopped during first trimester of pregnancy.
[b] Neonates with malformations / total number of exposed neonates.

The evaluation of healthcare resource utilization in newborns and in matched controls is the main added value of this study [15]. Cases exposed in utero to AEDs received slightly more drugs/prescriptions and had a greater likelihood of needing to be visited by a child psychiatrist (particularly those exposed to valproic acid). The rate of access to a child neuropsychiatry unit remained higher even after adjusting the analysis for malformations and weight for gestational age and may indicate a potentially greater risk of developmental disorders suggesting the need for further studies.

Wurtz et al. [16] evaluated the use of primary healthcare resources of children exposed prenatally to AED, such as the number of general practitioner contacts, and reported only small differences.

Finally, the finding that valproic acid was the second most used AED in pregnant women may have been influenced by the available data that are rated according to European Medicines Agency (EMA) warnings. This suggests that monitoring should be continued for a long period.

In conclusion, our results confirm the increased risk of malformations in children exposed to AEDs, mainly to valproic acid. A relationship with dose may exist. No differences emerged in healthcare resource utilization (i.e., in health status) between infants exposed to AEDs and controls, except for more frequent attendance at neuropsychiatric units. This needs further investigations. Thus, systematic monitoring of outcomes during the development of children exposed to AEDs during pregnancy is necessary.

## Author contributions

All the authors contributed equally to the design of the study. DP was involved in planning the data analysis and wrote the first draft of the manuscript. AC contributed in planning the data analysis and in writing the manuscript. RC undertook the statistical analysis. AngB, IF, and LM were involved in the data collection and management. AC, MPC, AV, DB, EB, EP, and MB supervised the study. All authors contributed to and have approved the final manuscript.

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## Disclosure of conflicts of interest

None of the authors have conflicts of interest associated with the subject of this publication.

**Table 2**
Healthcare utilization during the first year of life in cases exposed to all AEDs and to valproic acid only vs controls.

| Outcome at 1st year of life | All AEDs | | | Valproic acid | | |
|---|---|---|---|---|---|---|
| | Cases N = 526 | Controls N = 3682 | OR [95% CI] | Cases N = 131 | Controls N = 917 | OR [95% CI] |
| Hospitalizations | | | | | | |
| Number of hospitalized infants | 97 (18.4%) | 608 (16.5%) | 1.14 [0.90–1.45] | 24 (18.3%) | 157 (17.1%) | 1.09 [0.68–1.75] |
| Number of hospitalizations | 163 | 860 | 0.23* | 49 | 245 | 0.61* |
| Specialist visits | | | | | | |
| Number with ≥1 prescriptions | 391 (74.3%) | 2663 (72.3%) | 1.11 [0.90–1.37] | 101 (77.1%) | 671 (73.2%) | 1.23 [0.80–1.90] |
| Child neuropsychiatry | 40 (7.6%) | 166 (4.5%) | 1.74 [1.22–2.49] | 15 (11.5%) | 44 (4.8%) | 2.57 [1.38–4.76] |
| Number of prescriptions | 1349 | 8833 | 0.20* | 364 | 2191 | 0.23* |
| Child neuropsychiatry | 99 | 507 | 0.33* | 45 | 108 | 0.19* |
| Diagnostic tests | | | | | | |
| Number with ≥1 tests | 474 (90.1%) | 3343 (90.8%) | 0.92 [0.67–1.25] | 120 (91.6%) | 836 (91.2%) | 1.06 [0.55–2.04] |
| Number of tests | 2945 | 17,825 | 0.35* | 685 | 4370 | 0.9997* |
| Drug prescriptions | | | | | | |
| Number with ≥1 prescription | 350 (66.5%) | 2374 (64.4%) | 1.09 [0.90–1.33] | 92 (70.2%) | 602 (65.6%) | 1.23 [0.83–1.84] |
| Number of prescriptions | 1437 | 8241 | 0.03* | 418 | 2006 | 0.04* |

* p-Value of *t*-test (cases versus controls).

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DB has received honoraria for advisory boards from Sanofi-Aventis.

DP, AC, RC, MB, AB, IF, and LM have no conflict of interest to declare.

## Ethical approval

For this type of study, formal consent is not required.

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