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ORIGINAL RESEARCH ARTICLE

Gabapentin and Pregabalin Use in First Trimester of Pregnancy and Risk of Specific Congenital Anomalies: An IMI ConcePTION European Case-Malformed Control Study

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Abstract

Introduction and objective Given the increasing use of gabapentinoids and ongoing safety concerns, we assessed the association between first-trimester exposure to gabapentin and pregabalin and the risk of specific congenital anomalies (CAs) in the offspring.

Methods Using EUROmediCAT data, we conducted a case-malformed control study based on 170,126 registrants with major CAs from livebirths, fetal deaths (≥20 weeks), and terminations of pregnancy for fetal anomaly in nine European countries (2000–2020), covering 10.6 million births. We compared gabapentinoid use in registrants with a specific CA with those among other registrants with non-genetic CA (main control group) and among registrants with a genetic condition (secondary control group). We estimated odds ratios (OR) and 95% confidence intervals (CI), adjusting for registry, birth year, and maternal age. Analyses included specific subgroups of CA with ≥3 exposed registrants.

Results First-trimester gabapentinoid exposure was identified in 37 registrants, with most registered in the Valencian region (Spain) (37.8%), EFEMERIS (France) (13.5%) and three other registries (8.1% each). Over 60% of the exposures were observed during 2015–2020. Seven out of 91 EUROCAT subgroups had ≥3 exposed registrants: congenital heart defects, ventricular septal defects, severe congenital heart defects, limb anomalies, urinary anomalies, genital anomalies, and hypospadias. A significantly higher proportion of exposure (0.4‰, 12 exposed cases) was observed among cases with ventricular septal defect compared with registrants in the non-genetic control group (0.2‰, 17 exposed cases), with an adjusted OR of 2.5 (95% CI 1.1–5.3); and the adjusted OR was elevated but non-significant compared with the registrants in the genetic group (2.3; 95% CI 0.8–6.9).

Conclusions We observed an association between first trimester exposure to gabapentinoids and ventricular septal defect, the most common cardiac anomaly, although this finding is based on only 37 exposed registrants. While our findings align with some previous studies suggesting teratogenic risks associated with gabapentinoids, they also reveal the challenges of studying rare exposures and rare outcomes.

1 Introduction

Gabapentinoids (gabapentin and pregabalin) are GABA (gamma-aminobutyric acid) analogs. These compounds interact with multiple targets in neurons. They bind with high affinity to a protein in cortical membranes with an amino acid sequence identical to that of the α2-δ1 subunit of Ca*V*, the voltage-gated Ca2+ channel [2], thereby reducing the nerve cells' excitability in the brain. Gabapentin was first approved in Europe in 1993 for the treatment of epilepsy and

Key Points

An association with ventricular septal defects (cardiac anomaly) was observed, based on a small number of exposed cases, and should therefore be interpreted cautiously as hypothesis generating.

These findings highlight the need for cautious use of gabapentinoids in women of childbearing age and for further large-scale studies to better characterize their safety during pregnancy.

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neuropathic pain, while pregabalin, first approved in 2004, was additionally licensed for generalized anxiety disorder.

Gabapentinoids cross the placenta via active transport mechanisms [3, 4]. This raises concerns about their potential impact on embryo-fetal development, particularly during the first trimester, when organogenesis occurs. The α2-δ1 subunit to which gabapentinoids bind is expressed not only in the cerebral cortex but also in the heart and skeletal muscles, suggesting the possibility of off-target effects in non-neuronal tissues during critical developmental periods [5]. Their ability to affect multiple tissues, including the brain, heart, and skeletal muscles, underscores the need for caution and further investigation into their safety profile during pregnancy.

Since 2000, the use of gabapentinoids has significantly risen in the general population [6], including among pregnant women. For instance, a study showed a marked increase in gabapentin use among pregnant women, especially in the United States, from around 4.0 per 1000 in 2006 to 12.0 per 1000 in 2016 [7]. In the United Kingdom (UK), prescriptions of pregabalin and gabapentin among pregnant women rose from around 0.3 per 1000 in 2007 to 2.5–3.0 per 1000 in 2016, with around one-seventh of these prescriptions likely for pain management [8]. A similar, though less pronounced, trend was observed in France, where the prevalence of pregabalin use rose from 0.5 to 1.2 per 1000 pregnant women over the same period [8]. Recent European data further confirm that gabapentinoids are predominantly prescribed for anxiety and neuropathic pain rather than epilepsy among pregnant women [9]. In addition, up to 22% of pregnancies exposed to gabapentinoids in Wales suffered from alcohol withdrawal or substance use disorders, highlighting the potential for misuse and abuse of these medications and complex potential co-exposures [9].

Recent human studies have reported associations between gabapentin and pregabalin use during pregnancy and adverse pregnancy outcomes [10–17]. These safety concerns have prompted regulatory agencies to advise against the use of pregabalin and gabapentin during pregnancy unless the benefits clearly outweigh the potential risk to the fetus [18, 19]. A recent systematic review [20] highlighted increased risks of specific congenital anomalies (CAs) associated with pregabalin use [10], including those affecting the nervous system, eyes, oro-facial clefts, and genital organs, as well as coarctation of aorta following pregabalin monotherapy exposure (crude odds ratio [OR] 5.8; 95% confidence interval [CI] 1.6–14.9), based on four exposed cases [11]. In contrast, no increased risk was observed with gabapentin exposure.

The rising use of gabapentinoids, coupled with limited data on their safety during pregnancy, underscores the need for large-scale studies to investigate their potential associations with congenital malformations. The EUROmediCAT database provides a robust platform for this purpose, offering comprehensive and high-quality data on CAs. The aim of the present study was to assess the association between first-trimester exposure to gabapentin and pregabalin and the risk of specific CAs in offspring.

2 Materials and Methods

2.1 Study Design

We used data from EUROCAT [21] (the European network of congenital anomalies registries), as provided to the EUROmediCAT central database. This included data from registries that record medication use during pregnancy, as well as equivalent data extracted from the EFEMERIS healthcare database (France) [22]. These databases hold information on babies/fetuses with a major CA among live births (LB), fetal deaths (FD) of >20 completed weeks of gestation, and termination of pregnancy for fetal anomaly (TOPFA) at any gestational age [23]. The EUROmediCAT data source has successfully been used to assess association between maternal medication exposure and occurrence of CAs in the fetus/infant [24–26]. Major CAs were defined as structural abnormalities with significant medical, surgical, social, or cosmetic consequences for the affected individual. Importantly, the databases do not include any data on babies/fetuses without a CA. To avoid confusion regarding case/control status, we used the term "registrants" throughout the text for each individual record in the dataset. Consequently, we conducted a case-control study using malformed controls, comparing gabapentinoid exposure among registrants with a specific CA with gabapentinoid exposure among all other registrants. In other words, this approach aimed to assess whether exposure to gabapentinoids was more frequently recorded among registrants with a specific CA (cases) than among registrants with other non-genetic CA (controls).

2.2 Study Population and Data

The initial EUROmediCAT central database included data from 15 registries in 12 European countries covering 12 million births 1995–2020, to which were added the data from 145,000 births from EFEMERIS.

CAs are coded using the British Pediatric Association Classification of Diseases, Ninth Revision (ICD9-BPA) or Tenth Revision (ICD10-BPA) and classified into 91 standard "EUROCAT subgroups", as set out in the EUROCAT Guide 1.4 [27]. These include hierarchical subgroups; for example, spina bifida is a subgroup that forms part of the subgroup "neural tube defects," which forms part of the group "nervous system anomalies." Minor CAs listed in EUROCAT

Guide 1.4 are not reported [27]. The data on CAs varied across registries and was derived from maternity, neonatal, pediatric, fetal medicine, cytogenetic, pathology, and medical genetics records. The majority of the registries record anomalies diagnosed up to at least 1 year of age. Supplementary Table 1 shows the list of participating registries and healthcare databases, the years and number of births covered, along with the number of registrants with major CAs included in the study (see electronic supplementary material [ESM]).

2.3 Case and Control Definition

For each analysis, we considered registrants affected by a single non-genetic EUROCAT subgroup of CA to be the "case" group. We used two control groups: (i) "Non-genetic controls" were the remaining registrants with non-genetic CAs after exclusion of the specific CA being analyzed as the case group and of any subgroup at a hierarchical level above; (ii) "Genetic controls" included registrants with genetic syndromes, chromosomal anomalies, and pathogenic copy number variations such as microdeletions. Specifying a genetic control group, which cannot have been caused by environmental teratogens, is a commonly used approach in studies conducted within the EUROmediCAT database [25]. Hence, analyses were conducted subgroup by subgroup.

2.4 Exclusions

Registrants with isolated hip dislocation anomaly were excluded as it has a non-teratogenic etiology. Registrants with maternal use of known major teratogens (valproic acid, retinoids, immunosuppressants, oral anticoagulants and antimitotics) during the first trimester of pregnancy were also excluded (n = 569 registrants). Supplementary Table 2 shows the complete list.

The following additional exclusions were made:

- TOPFAs from the Emilia Romagna (n = 2,121) and Valencian region registry (n = 2,037 registrants), as it was not possible to link medications data to women having TOPFAs due to a privacy issue;
- Years 1995–2002 and 2014–2020 in the Tuscany registry, as prescription data were only available for 2003–2013 (n = 8,622 registrants);
- Years without maternal exposure to any gabapentinoids (1995–1999) in any registry (n = 9,934 registrants);
- Registries without any registrants with maternal exposure to gabapentinoids (Zagreb-Croatia, Saxony Anhalt-Germany, Wielkospolska-Poland and Malta) (n = 34,634);
- Registrants with maternal age not recorded (n = 22,392).

2.5 Exposure Definition

Maternal medication exposures in the first trimester of pregnancy were obtained retrospectively from prospective maternity records, medical records of the infant, and maternal interviews before or after birth. Concerning the Valencian region, Emilia Romagna and Tuscany registries, as well as the EFEMERIS data source, maternal medication exposures were based on linkage with prescription redemption records.

All medication exposures in the first trimester are recorded using the World Health Organization's Anatomical Therapeutic Chemical classification system (ATC). We defined exposure to gabapentin (ATC code: N03AX12) or pregabalin (ATC code: N03AX16) as use or dispensing of these medications during the first trimester of pregnancy (from the first day of the last menstrual period to the end of gestational week 12). Exposure to gabapentin or pregabalin was identified using a combination of ATC codes and keyword searches in free-text medication fields. All potentially exposed registrants underwent case-by-case validation by the registries based on original medical records to confirm first-trimester exposure and correct possible misclassification.

2.6 Statistical Analysis

2.6.1 Description of the Study Population

Characteristics of the study population were described in categories: registry, year of birth (2000–2004, 2005–2009, 2010–2014, 2015–2020), age of the mother at birth (<20, 20–29, 30–39, >40 years), birth type (LB, FD, and TOPFA), sex of the fetus/child, length of gestation in LB (<28, 28–31, 32–36, 37–41, and >41 weeks), low birth weight in LB (<2500 grams), multiple birth, and exposure to specific medications (antidepressants and benzodiazepine derivates, anti-seizure medications and clobazam, specific and non-specific pain medications; ATC codes are provided in Table 1). Categorical variables were described as numbers with percentage.

2.6.2 Analyses of Associations Between Gabapentinoids Exposure and Specific Congenital Anomalies (CAs)

We conducted a case-malformed control study where we estimated odds ratios (ORs) and their 95% confidence intervals (CI). This analysis compared the odds of exposure in registrants with specific non-genetic congenital subgroups

of anomalies (cases) to the odds of exposure among registrants with another non-genetic CA or genetic CA (controls), using logistic regression models. Reporting odds ratios (RORs) were subsequently adjusted for registry, birth year and maternal age. We performed a complete case analysis, therefore registrants with missing data for any of the adjustment covariates were excluded from the multivariable analyses. For the analysis of CA subgroups with five or fewer exposed cases, a bias correction was performed using the Firth method. In analyzing hypospadias cases, we only included male registrants. Only CA subgroups where the number of exposed registrants to gabapentinoids was three or greater were analyzed.

We performed analysis for gabapentinoid medications as a class, then we analyzed gabapentin and pregabalin separately. In analyses of exposure to gabapentin, registrants who had been exposed to pregabalin were excluded from the controls. Similarly, in analyses of exposure to pregabalin, registrants exposed to gabapentin were excluded from the controls.

A 2-sided 5% level of significance was applied. All statistical analyses were conducted in R studio version 2023.03.1.

2.6.3 Case Series

We compiled a case series to describe the characteristics of registrants exposed to gabapentinoids. Individual characteristics were reported such as birth year, description of CA, origin (multiple or isolated), timing of anomaly detection, gestational age at birth, birth weight, maternal illness before and during pregnancy, and maternal medications taken during the first trimester.

3 Results

3.1 Study Population

The initial data set consisted of 254,146 registrants with a CA, from 16 data sources across Europe for 26 years of birth (1995–2020). After applying exclusion criteria, our study population included 170,126 registrants from 12 data sources in nine countries from the period 2000 to 2020 (Fig. 1). A total of 37 (0.2‰) registrants were exposed in utero during the first trimester of pregnancy to at least one gabapentinoid medication. Our study population was divided into two groups: non-genetic CA registrants ($n = 146,233$), with 11 exposed to gabapentin and 20 to pregabalin; and genetic CA registrants ($n = 23,893$), with three exposed to pregabalin and three to gabapentin. No registrants were exposed to both medications.

3.2 Characteristics of the Study Population

Most of the exposed registrants were from the Valencian region (Spain) ($n = 14$, 37.8% of all exposed registrants), EFEMERIS (France) ($n = 5$, 13.5%) and La Réunion (France), Emilia Romagna (Italy), and the Northern Netherlands with three exposed registrants in each. More than 60% of the exposed registrants were observed in 2015–2020. Gabapentinoid exposure seemed more common among mothers over 30 years old, multiple pregnancies, and preterm births (gestational length <37 weeks) and registrants with a low birth weight (<2500 g) as compared with non-genetic registrants. Antidepressants and benzodiazepine derivates were reported among 21.6% of the mothers exposed to gabapentinoids, pain-specific medications were reported among 18.9%, while none reported the use of any other anti-seizure medication. The details of these characteristics are shown in Table 1.

3.3 Associations Between Specific Type of CA and Gabapentinoids Exposure

Only two EUROCAT subgroups had three or more registrants exposed to gabapentin (congenital heart defects [$n = 6$] and ventricular septal defect [$n = 5$]). The results were not significant for ventricular septal defect and gabapentin exposure even though the ORs were elevated when comparing with other non-genetic cases (adjusted ROR 2.6; 95% CI 0.8–8.3) (Table 2). Concerning pregabalin exposure, only four EUROCAT subgroups had three or more exposures: congenital heart defects ($n = 10$), severe congenital heart defects ($n = 3$), ventricular septal defect ($n = 7$), and urinary anomalies ($n = 3$). The results were not significant even though the ORs for ventricular septal defect were elevated when compared with other non-genetic cases (adjusted OR 2.4; 95% CI 0.8–6.4) (Table 2).

When grouping both medications together, seven of the 91 EUROCAT CA subgroups had three or more gabapentinoid-exposed registrants (Supplementary Table 3, ESM). These subgroups included congenital heart defects, ventricular septal defect, severe congenital heart defects, limb anomalies, urinary anomalies, genital anomalies, and hypospadias. A significantly higher proportion of exposure to any gabapentinoid (0.4‰, 12 exposed cases) was observed among cases with ventricular septal defect compared with the registrants in the non-genetic control group (0.2‰, 16 exposed cases), with an adjusted OR of 2.5 (95% CI 1.1–5.3), while the adjusted OR associated with the genetic controls was elevated but not significant (0.2‰, 6 exposed cases, adjusted OR 2.3, 95% CI 0.8–6.9) (Fig. 2 and Supplementary Table 4 [ESM] reporting all counts and crude ORs). Based on three or four exposed registrants, the ORs for severe congenital heart defects, genital anomalies, and

Table 1 Description of the characteristics of the study population: non-genetic registrants, genetic controls, and registrants exposed in utero to pregabalin or gabapentin

Maternal/fetal characteristic	Non-genetic registrants $N = 146,233$ n (%)	Genetic controls $N = 23,893$ n (%)	Registrants exposed to gabapentinoids[d] $N = 37$ n (%)
Registry/healthcare database			
Belgium, Antwerp	8215 (5.6)	1857 (7.8)	<3
Denmark, Odense	2272 (1.6)	644 (2.7)	<3
France, EFEMERIS[a]	3175 (2.2)	580 (2.4)	5 (13.5)
France, Paris	11,980 (8.2)	4254 (17.8)	<3
France, La Reunion	5785 (4.0)	1262 (5.3)	3 (8.1)
Ireland, Cork and Kerry	3055 (2.1)	1148 (4.8)	<3
Italy, Emilia Romagna[a]	9062 (6.2)	999 (4.2)	3 (8.1)
Italy, Tuscany[a]	5623 (3.8)	1293 (5.4)	<3
Netherlands, Northern	6821 (4.7)	2116 (8.9)	3 (8.1)
Poland, excluding Wielkopolska	80,615 (55.1)	7818 (32.7)	<3
Spain, Valencian region[a]	5069 (3.5)	547 (2.3)	14 (37.8)
Switzerland, Vaud	4561 (3.1)	1375 (5.8)	<3
Calendar year of birth			
2000–2004	25,657 (17.5)	4214 (17.6)	<3
2005–2009	34,409 (23.5)	6192 (25.9)	<3
2010–2014	40,268 (27.5)	6567 (27.5)	12 (32.4)
2015–2020	45,899 (31.4)	6920 (29.0)	23 (62.2)
Maternal age group (years)			
<20	5172 (3.5)	397 (1.7)	0
20–29	67,080 (45.9)	6293 (26.3)	8 (21.6)
30–39	67,578 (46.2)	12,775 (53.5)	23 (62.2)
>40	6403 (4.4)	4428 (18.5)	6 (16.2)
Type of birth			
Livebirth	139,373 (95.3)	15,272 (63.9)	35 (94.6)
Stillbirth/fetal death	1200 (0.8)	565 (2.4)	<3
Termination of pregnancy for fetal anomaly	5656 (3.9)	8056 (33.7)	<3
Not known	4 (0.0)	0 (0.0)	0
Biological sex			
Female	59,194 (40.8)	11,538 (49.5)	15 (41.7)
Male	85,679 (59.1)	11,727 (50.3)	21 (58.3)
Indeterminate	201 (0.1)	27 (0.1)	0 (0.0)
Missing	1159 (0.0)	601 (0.0)	1
Multiple birth			
Multiple birth	6148 (4.3)	701 (3.0)	5 (13.5)
Missing	3544 (0.0)	291 (0.0)	0
Low birth weight among livebirths			
<2500 grams	21,427 (15.4)	4031 (26.4)	11 (31.4)
Missing	18 (0.0)	0 (0.0)	0
Gestational length (weeks) among live births			
<28	1190 (0.9)	115 (0.8)	<3
28–31	3218 (2.3)	389 (2.5)	<3
32–36	17,128 (12.3)	2806 (18.4)	10 (28.6)
37–41	107,911 (77.4)	11,094 (72.6)	24 (68.6)
>41	9920 (7.1)	868 (5.7)	0 (0.0)
Missing	6 (0.0)	0 (0.0)	0
Exposure to some specific medications			
Antidepressants and benzodiazepine derivates (N06A, N05BA)	1114 (0.8)	207 (0.9)	8 (21.6)

Table 1 (continued)

Maternal/fetal characteristic	Non-genetic registrants $N = 146,233$ n (%)	Genetic controls $N = 23,893$ n (%)	Registrants exposed to gabapentinoids[d] $N = 37$ n (%)
Anti-seizure (other than gabapentinoids) and clobazam (N03, N05BA09)	280 (0.2)	43 (0.2)	0 (0.0)
Pain-specific medication[b]	274 (0.2)	65 (0.3)	7 (18.9)
Non-specific pain medication[c]	336 (0.2)	61 (0.3)	3 (8.1)
No maternal medication use reported	76,837 (52.5)	14,504 (60.7)	0 (0.0)

<3: Cells with <3 were masked, due to data privacy

[a]These registries/healthcare databases linked their congenital anomaly cases to prescription data

[b]Pain-specific medications: tramadol (N02AX02), capsaicin (N01BX04), lidocaine plaster (N01BB02), morphine (N02AA01), oxycodone (N02AA05), tapentadol (N02AX06), ziconotide (N02BG08), and other strong opioids (N02A);

[c]Non-specific pain medication: amitriptyline (N06AA09), clomipramine (N06AA04), imipramine (N06AA02), venlafaxine (N06AX16), duloxetine (N06AX21), botulinum toxin A (M03AX01), nortriptyline (N06AA10), carbamazepine (N03AF01), and methadone (N07BC02)

[d]Includes 31 non-genetic and 6 genetic registrants

hypospadias were raised when compared with the non-genetic and genetic controls, even though the CIs included the null (Fig. 2 and Supplementary Table 4 [ESM] reporting all counts and crude ORs).

3.4 Case Series

The detailed description of the case series is provided in Supplementary Table 5 (see ESM). We individually reviewed the records of all 37 registrants exposed to gabapentinoids in utero. Among these, only two registrants presented with multiple congenital anomalies: one involving a ventricular septal defect and a digestive system anomaly (imperforate anus), and the other a ventricular septal defect alongside a genital anomaly (hypospadias). For registrants with isolated anomalies, cardiac anomalies were the most frequent, occurring in 38% ($n = 14$) of cases. Among these, ventricular septal defects were predominant, identified in 12 registrants. Six registrants involved an isolated ventricular septal defect, while the remaining cases had additional cardiac malformations such as atrial septal defect, transposition of the great vessels, and coarctation of the aorta.

Analysis of maternal illness reported in the records provided insights into the potential reasons for gabapentinoid use. Pain-related conditions, including chronic pain, fibromyalgia, facial neuralgia, and osteochondrodysplasia were documented in 19% ($n = 7$) of the registrants. Anxiety and depression were noted in 14% ($n = 5$), and epilepsy was reported in two registrants. Additionally, multiple sclerosis was mentioned in 8% ($n = 3$) of the records, and migraine was noted in one registrant. No maternal disease was reported in 35% of registrants ($n = 13$).

4 Discussion

4.1 Main Findings

Among the 170,126 registrants with CA across Europe, reported exposure to gabapentinoids during the first trimester of pregnancy was infrequent, with only 37 cases reported in this large dataset. Despite this low number, our analysis identified a two-fold increased risk between first-trimester gabapentinoid exposure and ventricular septal defect, a specific type of cardiac anomaly (adjusted OR 2.5, 95% CI 1.1–5.3).

4.2 Comparison with Existing Literature

Animal studies have linked prenatal exposure to gabapentin with adverse fetal outcomes, such as fetal growth retardation and increased incidence of hydroureter, hydronephrosis and fetal loss [28, 29], while pregabalin has been linked to an increased incidence of skeletal anomalies [30]. In human studies, gabapentin and pregabalin use during pregnancy has been associated with increased risks of adverse pregnancy outcomes, including specific anomalies affecting the nervous

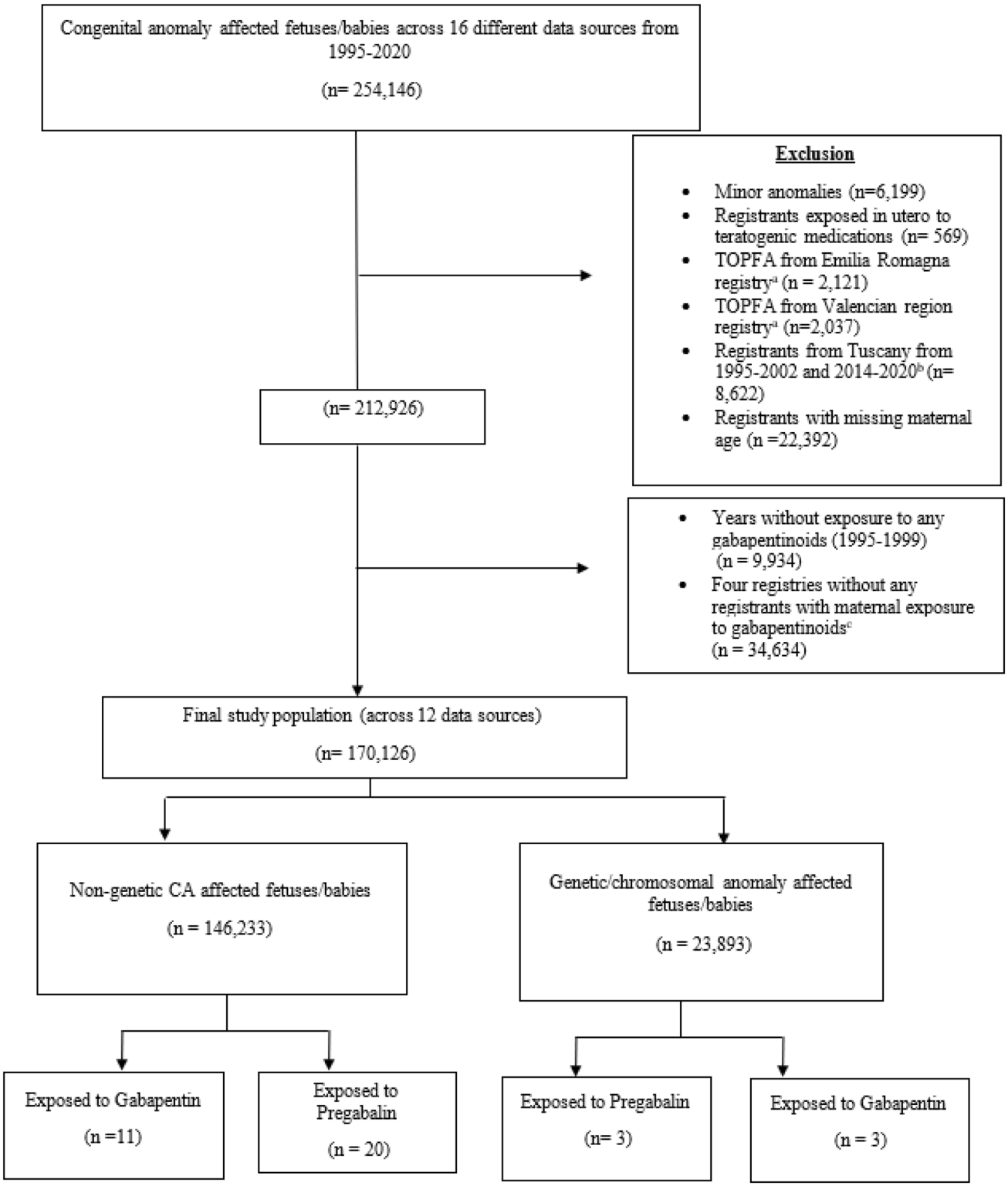

Fig. 1 Flowchart of the population. [a] Information on medication is only available for livebirths and fetal death. [b] Verified exposures are only available for the years 2003–2013. [c] Zagreb (Croatia), Saxony Anhalt (Germany), Wielkospolska (Poland), and Malta. *CA* congenital anomaly, *TOPFA* termination of pregnancy for fetal anomaly

Table 2 Crude and adjusted ORs for the association between gabapentin and pregabalin exposure during the first trimester of pregnancy and CA subgroups

Congenital anomaly subgroup of interest	Cases		Controls							
			Non-genetic				Genetic			
	Total cases[a]	Exposed cases n (%)	Total controls[a,b]	Exposed controls n (%)	Crude OR (95% CI)	Adj OR[c] (95% CI)	Total controls[a]	Exposed controls n (%)	Crude OR (95% CI)	Adj OR[c] (95% CI)
Gabapentin										
Congenital heart defects	52,234	5 (0.01)	93,979	6 (0.01)	1.52 (0.49–4.74)[d]	1.44 (0.46–4.52)[d]	23,890	3 (0.01)	0.72 (0.19–2.75)[d]	1.07 (0.26–4.36)[d]
Ventricular septal defect	28,476	5 (0.02)	93,979	6 (0.01)	2.79 (0.90–8.69)[d]	2.62 (0.83–8.30)[d]	23,890	3 (0.01)	1.32 (0.35–5.04)[d]	2.36 (0.57–9.83)[d]
Pregabalin										
Congenital heart defects	52,239	10 (0.02)	93,983	10 (0.01)	1.80 (0.74–4.38)	1.72 (0.70–4.26)	23,890	3 (0.01)	1.52 (0.47–6.80)	1.62 (0.45–7.85)
Ventricular septal defect	28,478	7 (0.02)	93,983	10 (0.01)	2.31 (0.84–6.02)	2.37 (0.84–6.41)	23,890	3 (0.01)	1.96 (0.54–9.08)	2.06 (0.52–10.32)
Severe congenital heart defects	11,845	3 (0.03)	93,983	10 (0.01)	2.65 (0.79–8.87)[d]	2.87 (0.85–9.73)[d]	23,890	3 (0.01)	2.02 (0.46–8.88)[d]	2.14 (0.45–10.09)[d]
Urinary anomalies	22,293	3 (0.01)	123,929	17 (0.01)	1.11 (0.35–3.50)[d]	0.81 (0.26–2.57)[d]	23,890	3 (0.01)	1.07 (0.24–4.72)[d]	1.04 (0.21–5.08)[d]

[a]Complete cases

[b]No of controls used in each analysis varied according to exclusion of case group and congenital anomaly subgroup at hierarchical level above where relevant

[c]Adjusted for registry, calendar year and maternal age

[d]Firth bias correction; gabapentin analysis excluded pregabalin exposure and pregabalin analysis excluded gabapentin exposure

CA congenital anomaly, *CI* confidence interval, *OR* odds ratio

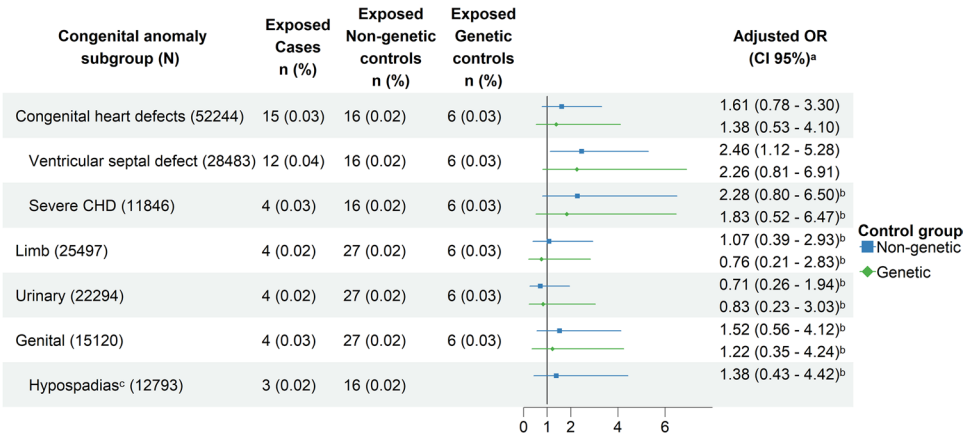

Fig. 2 Adjusted OR for the association between gabapentinoids exposure during the first trimester of pregnancy and CA subgroups. Results are based on a complete cases analysis. [a]Adjusted for registry, calendar year, and maternal age. [b]Firth bias correction. [c]Only among male registrants. *CA* congenital anomaly, *CI* confidence interval, *OR* odds ratio

system, eyes, oro-facial clefts, and genital organs, as well as coarctation of aorta [10, 11, 15].

Regarding cardiac anomalies, previous studies have not identified an increased risk of ventricular septal defect after prenatal exposure to pregabalin or gabapentin. Although sensitivity analyses restricted to isolated anomalies were not performed due to the limited number of exposed cases, most ventricular septal defects observed among exposed pregnancies were isolated, which may support the consistency of the observed association. However, heterogeneity across phenotypic presentations cannot be fully excluded. Our results suggest an association with this anomaly when the medications are considered together. Taken separately, we found no significant association, likely due to the small number of exposed registrants with this specific anomaly (five congenital heart defects cases exposed to gabapentin and 10 exposed to pregabalin). Notably, the point estimates for gabapentin (adjusted OR 2.6) and pregabalin (adjusted OR 2.47) were consistent with those where medications are combined (adjusted OR 2.5). A study using data from the French National Health Data System, which covers 99% of the French population, reported an increased risk of coarctation of the aorta, which is a cardiac anomaly, following pregabalin monotherapy compared with unexposed pregnancies (crude OR 5.8, 95% CI 1.6–14.9) [11], although it was based on only four exposed cases and without adjustment for covariates. Concerning gabapentin exposure, two studies have identified an increased risk of cardiac anomalies. The first one, using the United States Medicaid Analytic eXtract database (over 1.7 million pregnancies), reported an increased risk of major cardiac anomalies associated with first trimester exposure to gabapentin compared with unexposed pregnancies (crude RR 1.8, 95% CI 1.4–2.2; 87 exposed cases) [15]. However, this risk was not significant after adjusting for confounding factors (adjusted RR 1.1; 95% CI 0.9–1.4) [15]. This study also identified an association with conotruncal defects, which are outflow tract defects (e.g., truncus arteriosus, tetralogy of Fallot, interrupted aortic arch, transposition of the great arteries and double outlet right ventricle) (adjusted RR 2.0, 95% CI 1.0–3.8) [15]. The authors did not find an elevated risk of ventricular septal defects (adjusted RR 0.9, 95% CI 0.6–1.3) [15], which contrasts with our results. The second study, a meta-analysis conducted in 2024, included data from Manitoba (Canada), France, and the United States, encompassing 6374 pregnancies exposed to gabapentin [16]. This analysis reported an increased risk of cardiac malformations compared with unexposed pregnancies (unadjusted RR 1.7, 95% CI 1.1–2.5; $n = 129$ exposed cardiac cases) [16]. However, the lack of adjustment for potential confounders in these results warrants caution.

Beyond cardiac anomalies, a large Nordic study from 2023 involving around three million pregnancies identified increased risks of CA affecting the nervous system (6 exposed cases), eyes (<5 exposed cases), oro-facial clefs (5 exposed cases), and genital system (<5 exposed cases) following pregabalin exposure during the first trimester of pregnancy [10], despite the small number of cases in each anomaly subgroup. A key strength of this study was its rigorous control of confounders and use of multiple comparator groups (active comparators) [10]. In our study, the limited number of exposed registrants prevented us from investigating these specific anomalies for pregabalin. When pregabalin and gabapentin were examined together, the differences with both control groups were not statistically significant and the limited number of exposed cases ($n = 4$) prevented us from concluding on any association. For gabapentin, our study lacked sufficient cases to evaluate specific CAs beyond cardiac anomalies.

Given that myocardial development predominantly occurs between the 2nd and 10th weeks of pregnancy, the binding of gabapentinoids to the α2-δ1 subunit, which is not only expressed in the cerebral cortex but also in the heart and skeletal muscles [5], could plausibly interfere with calcium signalling pathways essential for cardiac morphogenesis.

This mechanism highlights a potential pathophysiological basis for adverse effects on myocardial development.

4.3 Strengths and Limitations of the Study

The main strength of this study lies in the use of the large, international, population-based, EUROmediCAT central database, whose diverse nature enhances the generalisability of our findings. Also, we were able to pool the data from 12 registries to assess associations, it would not have been possible in individual registries due to small number of exposed cases. EUROmediCAT provides detailed and standardized coding of all CA among LB, FD, and TOPFA. The harmonized data set ensures comprehensive and standardized collection of both congenital anomaly and medication exposure data, minimizing potential biases. These findings also highlight the value of harmonized data collection across registries and health databases, as they enable researchers to pool data and increase statistical power for studying rare exposures and outcomes. In addition, we were able to assess association to specific CAs, not CA as a whole.

A significant advantage of the EUROmediCAT database is that medication exposure is mostly recorded prospectively, before anomaly status is known, which reduces the risk of recall bias. In certain registries, such as those in the Valencian region, Tuscany and Emilia Romagna, as well as the EFEMERIS data source, medication exposure data are derived from prescription records, adding an additional layer of reliability. Notably, these sources are among those where we observed the highest exposure to gabapentinoids. Furthermore, the inclusion of adjusted analyses in our study strengthens the validity of the findings by accounting for known confounders, although residual confounding cannot be entirely ruled out.

Despite these strengths, the study has several limitations. Previous studies, based on pharmacy claims, had estimated the prevalence of gabapentinoids during the first trimester of pregnancy as being from 0.2‰ to 1.2‰ in Europe [11, 14]. In our dataset, the prevalence was 0.2‰, which is in line with the lowest estimates, leading to only 37 exposed registrants. This small number of gabapentinoid-exposed registrants reduces statistical power, limiting our ability to detect associations for rare anomalies and contributing to wide CI in some analyses. Additionally, medication data were not available for TOPFA in the Emilia Romagna and Valencian Region registries (due to law restrictions), and linkage to medication data was available only for a limited time frame in the Tuscany registry. On the other hand, the low level of prenatal exposure in a population of malformed neonates may indicate that the risk of congenital anomaly related to gabapentinoid exposure is probably low.

For most registries, uncertainty remains regarding actual medication use, as mothers may not have taken the medication dispensed at the pharmacy, and exact timing within the first trimester is not recorded. The absence of detailed information on dosage, timing, and duration of gabapentinoid use restricts our ability to perform a more granular analysis. Furthermore, under-ascertainment of medication exposure, particularly for acute or non-chronic illness, of registries not linked with a prescription database is a known limitation in the EUROmediCAT database [31]. This under-ascertainment likely applies equally to cases and controls, which could have reduced the power of the study and slightly attenuated the observed estimates. Exposure ascertainment methods varied across registries, and medication data were not available for terminations for fetal anomalies in two registries. Although these registries contributed a substantial proportion of exposed cases, the limited number of exposed individuals overall precluded sensitivity analyses restricted to registries with complete exposure data, and differential exposure misclassification cannot be ruled out. We cannot exclude the presence of a nonspecific teratogen bias if gabapentinoids exposure is exposed to several congenital anomaly subgroups; some of which were included in the control group, leading to underestimation of the estimates [25, 32]. This will be mitigated by the use of the genetic control group, in which CAs are unlikely to be caused by gabapentinoids exposure, but as their numbers are small this reduces statistical power. Finally, information on maternal conditions was included in the database but was heterogenous across registries and limited in scope. The investigation of the maternal illness variables and the free-text data as part of the case series allowed us to gain some knowledge about the maternal condition of the exposed registrants. Pain-related conditions and anxiety were the most frequent conditions reported. Lastly, although we adjusted for several important confounders, the observational nature of this study implies that residual confounding cannot be excluded. Unmeasured factors, including underlying maternal health conditions, concurrent medication use (such as antiepileptics, antidepressants, or opioids), smoking, and alcohol consumption, may still partially account for the observed associations.

4.4 Implications

Our findings contribute to the growing body of evidence on the safety risk profile of gabapentinoids during pregnancy. The observed association between first-trimester exposure to gabapentinoids and ventricular septal defect should be interpreted cautiously, given the small number of exposed cases, and considered primarily as hypothesis generating. Nevertheless, even small potential risks may have public health relevance in the context of the increasing use of

gabapentinoids for chronic pain and other indications among women of childbearing age.

These findings support the need for healthcare providers to include potential CA risks in risk–benefit discussions with women. Previous research has linked pregabalin use during pregnancy with increased overall risks of CA, miscarriage, stillbirth, and specific neurodevelopmental outcomes [10–12], while gabapentin exposure has been associated with increased risks of preterm birth, preeclampsia, small-for-gestational-age, and admission to neonatal intensive care units [15, 16]. Given the increasing use of gabapentinoids during pregnancy, it is essential to consider fetal, infant, and maternal safety in a comprehensive manner. When gabapentinoid treatment is necessary, clinicians should carefully evaluate alternative therapies, consider additional fetal monitoring, and inform women about the potential risks.

From a research perspective, our study emphasizes the need for further investigation into the teratogenic effects of gabapentinoids, particularly focusing on specific CA and controlling for confounding factors. Future studies with larger sample sizes and robust study designs will be critical to confirm or refute the associations observed in our analysis and other recent studies.

5 Conclusion

In this large European study including 170,126 registrants with CA, we observed an association between first-trimester gabapentinoid exposure and ventricular septal defect. While our findings align with some previous studies suggesting teratogenic risks associated with gabapentinoids, they also reveal the challenges of studying rare exposures and outcomes, including limited statistical power and potential confounding factors. Our results underscore the importance of cautious prescribing of gabapentinoids to women of childbearing age and the need for further research to better characterize their safety profile during pregnancy.

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Declarations

Conflicts of interest XM has received financial support from Allergan-Abbvie, Amgen-Horizon, Aptyspharma, Biogen, BMS, Grünenthal, Lilly, Lundbeck, Teva, Merck-Serono, Novartis, Orion, Pfizer, Roche, Sanofi-Genzyme and Sun Pharma and non-financial support from Dr Reddy's and SOS Oxygène not related to the submitted work. All other co-authors have no competing interests to disclose.

Ethics approval Ethical approval for the EUROmediCAT database was provided by the Ulster University Nursing Research Governance Filter Committee. The EFEMERIS cohort was approved by the French Data Protection Agency on 7 April, 2005 (authorization number 05-1140). All contributing registries have their own ethics approval arrangements appropriate to their national and local ethics guidelines, and gave approval for their data to be used in this study. This study was performed on anonymized patient data.

Consent to participate All data in EUROmediCAT are anonymized; therefore, patient informed consent for this particular study was not required. The women included in EFEMERIS database were informed of their inclusion and of the potential use of their anonymized data for research purposes. They can oppose the use of their data at any time.

Consent for publication No specific consent for this publication was obtained from women.

Availability of data and material: EUROmediCAT encourages the use of its data and networks for pharmacovigilance and medication safety research. Individual data are only available to consortium members; however, EUROmediCAT can be commissioned to do a study, or engage in a collaborative study. Requests can be made at https://euromedicat.eu/research/howtoproposeorcommissionspecificstudies.

Code availability: The study protocol was registered in the EUPAS Registry (EUPAS43385) and is available from the zenodo repository: https://zenodo.org/record/7476130 [1]

Author contributions: The study was primarily conceived and designed by ABB and CDM. ML provided access to the EUROmediCAT Central Database. M-C A, JB, AC, EG, MG, JH, EDH, A L-B, NL, and MM reviewed and confirmed exposure and congenital anomalies classification of their exposed cases. EG and ML reviewed the congenital anomalies classification and provided input in the case series description. The data curation and statistical analyses were performed by ECC. ABB and ECC drafted the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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