ORIGINAL RESEARCH ARTICLE

Signal Detection in EUROmediCAT: Identification and Evaluation of Medication–Congenital Anomaly Associations and Use of VigiBase as a Complementary Source of Reference

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Abstract

Introduction Knowledge on the safety of medication use during pregnancy is often sparse. Pregnant women are generally excluded from clinical trials, and there is a dependence on post-marketing surveillance to identify teratogenic medications.

Aims This study aimed to identify signals of potentially teratogenic medications using EUROmediCAT registry data on medication exposure in pregnancies with a congenital anomaly, and to investigate the use of VigiBase reports of adverse events of medications in the evaluation of these signals.

Methods Signals of medication–congenital anomaly associations were identified in EUROmediCAT (21,636 congenital anomaly cases with 32,619 medication exposures), then investigated in a subset of VigiBase (45,749 cases and 165,121 exposures), by reviewing statistical reporting patterns and VigiBase case reports. Evidence from the literature and quantitative and qualitative aspects of both datasets were considered before recommending signals as warranting further independent investigation.

Results EUROmediCAT analysis identified 49 signals of medication–congenital anomaly associations. Incorporating investigation in VigiBase and the literature, these were categorised as follows: four non-specific medications; 11 likely due to maternal disease; 11 well-established teratogens; two reviewed in previous EUROmediCAT studies with limited additional evidence; and 13 with insufficient basis for recommending follow-up. Independent investigations are recommended for eight signals: pregnen (4) derivatives with limb reduction; nitrofuran derivatives with cleft palate and patent ductus arteriosus; salicylic acid and derivatives with atresia or stenosis of other parts of the small intestine and tetralogy of Fallot; carbamazepine with atrioventricular septal defect and severe congenital heart defect; and selective beta-2-adrenoreceptor agonists with posterior urethral valve and/or prune belly.

Conclusion EUROmediCAT data should continue to be used for signal detection, accompanied by information from VigiBase and review of the existing literature to prioritise signals for further independent evaluation.

1 Introduction

Evidence from a multinational perspective suggests that, on average, 82% of women take at least one medication (excluding vitamins and minerals) in pregnancy [1, 2], with European studies reporting first trimester prescription medication usages from 35% in Norway [2] to 76% in France [3]. Yet,

knowledge on the safety of these medications in pregnancy is often sparse. Pregnant women are excluded from clinical trials, unless the medication is specifically aimed at pregnancy-related conditions. However, pregnant women do suffer from both acute and chronic conditions, and will therefore often need to take medications. It is also essential to have comprehensive information available about the safety of these medications because women may risk exacerbating their conditions and harming the foetus due to reducing their medication for fear of possible harmful effects to the foetus.

As limited evidence about the safety of these medications is available pre-marketing, there is a dependence on

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Key Points

EUROmediCAT can identify signals of potential teratogenic medications; existing literature must be evaluated before recommending further investigations.

Eight signals of medication–congenital anomaly associations are presented, which are considered to warrant further investigation in independent studies.

VigiBase provided supportive information for seven of the 11 signals of medication–congenital anomaly associations involving known teratogens, and although supportive for only one out of the eight signals warranting further investigation, VigiBase helped inform decisions when selecting these signals.

post-marketing surveillance. A study examining safety information for 173 medications approved by the FDA from 2000 to 2010 found that the teratogenic risk in human pregnancy was "undetermined" for 168 (97.7%), and for those medications approved between 1980 and 2000, the mean time for a treatment initially classified as having "undetermined" risk to be assigned a more precise risk was 27 years (95% confidence interval [CI] 26–28 years) [4]. Once a clinical suspicion about the teratogenicity of a medication has been raised, further evidence can be obtained from retrospective observational studies. Case control or cohort studies can be performed by either directly enrolling women into the study [5–7] (e.g. identifying women already enrolled in a teratology information service [8, 9]), or using routine sources of data [10–12] or data from specific pregnancy cohorts [13–16]. These studies often rely on the existence of an initial suspicion about a specific medication or a specific congenital anomaly (CA), which may be raised using spontaneous reporting systems. These reporting systems were originally established as a consequence of the thalidomide tragedy in the 1960s, and they collect spontaneous reports of suspected adverse drug reactions with the aim of raising early suspicions of previously unrecognised safety concerns [17]. However, data from spontaneous reporting systems do not enable the risk of a specific outcome to be quantified, as only adverse outcomes are reported, not unaffected outcomes.

EUROCAT is a network of European population-based CA registries; registries that record information on first trimester medication exposures are further eligible for inclusion in the EUROmediCAT database. EUROmediCAT developed a signal detection method where "signals" were defined as associations between pregnancy exposures and subsequent congenital anomalies in the foetuses that were unlikely to have arisen by chance [18]. This method does not determine causal pathways, but merely aims to identify associations that merit further investigation in independent studies. In 2016, the first set of signals was identified and, following data validation and literature reviews to identify prior evidence of human teratogenicity, six signals were determined to confirm existing evidence in the literature and seven signals were identified as requiring independent confirmation due to a lack of evidence in the literature [19]. Since 2016, improvements to the EUROmediCAT signal detection method have been developed [20] and more recent data have been added to the EUROmediCAT database.

VigiBase, the World Health Organization (WHO) global database of individual case safety reports, is the world's largest repository of spontaneous adverse event reports of medications and is a source of information on potentially teratogenic medications. VigiBase is regularly screened for statistical signals at Uppsala Monitoring Centre (UMC), using a method that combines multiple strength-of-evidence aspects in case series [21]. Signals thereafter undergo clinical assessment [22] to decide if there is enough basis to suggest further investigation [23]. There has been, to our knowledge, limited use of VigiBase in the context of medications used during pregnancy [24, 25].

The present study aimed (1) to identify and evaluate medication–CA association signals of potentially teratogenic medications using EUROmediCAT data and existing literature, and (2) to investigate the use of VigiBase as a complementary reference source in the evaluation of these signals.

2 Methods

The EUROmediCAT database was used to detect signals in medication exposures from 1995 to 2015. The resulting set of signals was then investigated by searching existing literature, requesting EUROmediCAT registries to confirm their cases and reviewing statistical reporting patterns and case series in VigiBase. Results from the two databases are presented and discussed together.

2.1 Detecting Signals in EUROmediCAT

2.1.1 EUROmediCAT Database

EUROCAT CA registries that collect information on medication exposures during the first trimester of pregnancy for cases (including live births, foetal deaths from gestational age 20 weeks and terminations of pregnancy for foetal anomalies) participate in EUROmediCAT. Each case has at least one major CA defined according to the EUROCAT Guide 1.4 [26], using the International Classification of Diseases (ICD) coding (versions 9 and 10) and the British Paediatric Association (BPA) adaptation, which gives supplementary

one-digit extensions to ICD-10 codes to allow greater specificity of coding. Each case may have an unlimited number of medication exposures, usually obtained from prospectively recorded maternity records [27] and coded using the WHO Anatomical Therapeutic Chemical (ATC) controlled hierarchical medication classification system [28]. ATC codes comprise up to seven digits, with the first five digits (ATC-4 level) representing chemical subgroups and all seven digits (ATC-5 level) representing chemical substances. Many registries provide additional information in text fields for each anomaly and each medication exposure. Other data collected for anomaly registrations, such as gestational age, time of diagnosis and outcome of the pregnancy, are described in detail in EUROCAT Guide 1.4 [26]. All data are standardised, and data quality indicators are applied to maintain accuracy. Ethical approval for the EUROmediCAT database was provided by the Ulster University Nursing Research Governance Filter Committee.

2.1.2 EUROmediCAT Signal Detection Dataset

Data on malformed cases with first trimester medication exposures from 1995 to 2015 were available from 21 CA registries in 15 European countries. The following exclusion criteria were applied to the dataset analysed in this study:

1. Cases with a chromosomal anomaly, skeletal dysplasia, or genetic syndrome were excluded from the data analysed, since the aetiology is assumed to not be teratogenic for the majority of these anomalies. In addition, all cases that had an isolated congenital dislocation of the hip were excluded, since the aetiology is assumed to be mechanical rather than teratogenic, and related to the third trimester. The use of chromosomal anomaly cases as controls is not optimal for signal detection due to concern that this believed lack of teratogenicity could lead to under-reporting of medications.
2. Cases with no known medication exposure in the first trimester or only exposed to folic acid, minerals and/or vitamins were excluded from the data analysed. In addition, cases with only medications coded with less than five digits (i.e. ATC-3 level or below) and cases with only topical medications (S01–S03, D01A, D02-D04, D05A, D06, D09, D10A, D11AA, D11AC, D11AE, D11AF, D11AH01, D11AH03, M02 and all D11AX codes except for the oral preparations [D11AX02 and D11AX10]) were excluded.

These criteria are the same as those applied in the first EUROmediCAT signal detection analysis [1, 18, 29]. The present study includes up to 4 new years of data from existing EUROmediCAT registries, and data from six additional registries (Saxony-Anhalt, Germany; South-East Ireland;

Isle de Reunion, France; Basque Country, Spain; Valencian Region, Spain; Ukraine) compared to the data in the original study analysed by Luteijn et al. [18].

2.1.3 Congenital Anomaly Groups Analysed

EUROCAT Guide 1.4 defines 90 CA subgroups that are used in routine CA surveillance [26]. Of these, individuals with a chromosomal anomaly (six subgroups), skeletal dysplasia or a genetic syndrome were excluded from the data, as described above. Of the remaining 82 EUROCAT subgroups, 15 were considered too heterogeneous to be informative when considering medication–CA associations. For example, ten of these EUROCAT subgroups are whole-organ systems (aggregating more specific EUROCAT subgroups) such as "Digestive", "Respiratory" or "Urinary". A further six subgroups were considered not applicable for analysis due to probable other causes, for example, "maternal infections resulting in malformations" includes specific maternal viral infections during pregnancy resulting in congenital anomalies in the foetus or infant. Therefore, medication associations were analysed in only 61 CA subgroups for the signal detection purpose of this study (see Supplementary Table 1 in the electronic supplementary material). Patients with an anomaly not in the 61 subgroups analysed and who had not been excluded due to them having a chromosomal anomaly, skeletal dysplasia or genetic syndrome were included as a "comparison anomalies" group. For example, a case with only the anomaly "indeterminate sex" specified was included in the anomaly comparison group in all analyses. Of the 61 anomalies analysed, three were aggregate groups: congenital heart defects (CHDs, 20 subgroups), severe CHDs (16 subgroups) and neural tube defects (NTDs, three subgroups); these aggregate groups were included because some medication exposures have shown association with several subgroups within these aggregate groups, for example, valproic acid is known to increase the risk of several heart defects including atrial septal defects and ventricular septal defects [30].

2.1.4 Medications Analysed

Analyses were performed using ATC-5 and ATC-4 level exposures separately, as in some cases, exposure information was only available at the ATC-4 level. EUROmediCAT registries do not generally have information on the duration or dosage of medication exposures. ATC codes subject to alterations over time are available on the WHO website, and older codes were updated to the newer code for all ATC-5 alterations noted up to the end of 2015, in order to capture any changes within the time period covered by the EUROmediCAT data [31]. ATC alterations with special notes were not considered, and no ATC-4 codes in the data were subject

to alterations. ATC coding is grouped according to therapeutic areas, and active substances used in more than one therapeutic area can therefore be classified with more than one ATC-code. For example, acetylsalicylic acid can be used as an analgesic (N02BA01), an antithrombotic (B01AC06) or a stomatological preparation (A01AD05). In EUROmediCAT, these multiple ATC-5 codes were grouped together using the most common ATC-5 code for that type of substance (i.e. N02BA01 in the above example). All medications with at least three exposed cases were investigated.

2.1.5 Statistical Methods in EUROmediCAT

The proportion of exposures to each specific medication in cases with a specific anomaly (numerator) was compared to the proportion of exposures to that medication in the anomaly comparison group (denominator), with estimates reported using the proportional reporting ratio (PRR) [32]. A double false discovery rate (FDR) [33, 34] procedure was used to adjust P values for multiple testing. This procedure consists of two stages to account for groupings of medications within pharmacological subgroups (using ATC-3 codes); firstly, a representative minimum P value is calculated for each ATC-3 medication group. In the second stage, only groups for which the representative P value is below a specified FDR threshold are retained, and a Simes FDR procedure [35] is then applied across all medication–CA combinations remaining in the process. The double FDR procedure was carried out separately for ATC-5 codes and ATC-4 codes. A selection process was then applied, whereby medication–CA combinations involving any of the following were removed: a truncated ATC-4 code of an ATC-5 code associated with the same anomaly, the aggregate anomaly of a more specific anomaly associated with the same exposure or an association with a PRR < 1. An association with a PRR< 1 indicates that fewer cases with the anomaly were exposed to this medication than expected, which does not indicate that the medication is protective (as comparisons are not to cases without anomalies). The current EUROmediCAT signal detection method [20] differs from that in the previous paper [18] in that PRRs are reported, whereas previously odds ratios were reported. To account for potential confounding by registry, adjusted Mantel-Haenszel estimates were calculated for each association passing double FDR and the signal selection process. Estimates for the abdominal wall defect gastroschisis were further adjusted for maternal age, since maternal age is known to be associated with both gastroschisis (higher risk in younger mothers) [36] and medication usage (higher in older mothers, particularly for chronic conditions) [1]. Most other non-chromosomal anomalies are not strongly associated with maternal age [37]. Remaining medication–CA associations were those considered to be statistical signals to be followed up in more

detail. Outcomes are reported using PRRs and corresponding 95% CIs; by definition, statistical signals have a lower limit of the two-sided 95% CI > 1. All analyses of EUROmediCAT data were conducted in Stata, version 13. A list of signals persisting after adjustment for registry (assessed by AC and JKM) was shared with investigators at UMC (LS, IÖ, KS and TB) for independent investigation in the VigiBase database.

2.2 Evaluating EUROmediCAT Signals in VigiBase

2.2.1 VigiBase Database

VigiBase contains over 22 million adverse event reports of medications submitted from 139 member countries of the WHO Programme for International Drug Monitoring (as of May 2020). The database dates back to 1968, with reports originating from different reporters including health professionals, consumers, and marketing authorisation holders, depending on the national pharmacovigilance system. Medications in VigiBase are coded to the international reference for medicinal product information, WHODrug [38], which is linked to the ATC classification system. Adverse events are mapped to terms in the Medical Dictionary for Regulatory Activities (MedDRA®), which has a hierarchical structure consisting of five levels: Lowest Level Term (LLT), Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and System Organ Classes (SOC).

2.2.2 VigiBase-CA Dataset

VigiBase includes case reports not only on CAs but any type of adverse event; thus, a subset of data was extracted to retrieve a VigiBase-CA dataset more closely corresponding to the EUROmediCAT signal detection dataset. The MedDRA® (version 20.1) SOC "Congenital, familial and genetic disorders", excluding certain HLTs describing hereditary/genetic disorders and infections, was used as the basis for the dataset (Supplementary Table 2 in the electronic supplementary material). Included reports had at least one adverse event term subordinated to any of these terms and at least one medication characterised as suspect or interacting. Medications are characterised by the primary reporter as suspect, interacting or concomitant; however, in UMC's statistical signal screenings, only reports with the medication characterised as suspect or interacting are included, which was the rationale for using the same approach in this study. The subset was further restricted to reports submitted to VigiBase between 1995 and 2017, reflecting the time period of the analysed EUROmediCAT data while accounting for delay of reporting to VigiBase. As in EUROmediCAT, reports describing a chromosomal anomaly, skeletal dysplasia, genetic syndrome or an isolated congenital dislocation of

the hip were excluded according to the definitions in Supplementary Table 3. Similarly, reports describing foetuses only exposed to folic acid and/or vitamins were also excluded.

In contrast to EUROmediCAT data, reports on topical medications were not excluded from the VigiBase-CA dataset. Medications in VigiBase may be linked to several different ATC groups, and formulations or routes of administration might not always be reported; thus, it was not feasible to consistently identify and thereby exclude medications only administered topically. The VigiBase-CA dataset was also not limited to reports on first trimester medication exposures because information on time of exposure is not consistently reported in a structured format in individual case safety reports. In addition, the VigiBase-CA dataset was not restricted to major malformations but included a wider scope of congenital disorders, as major malformations are not systematically grouped within the MedDRA® hierarchy.

2.2.3 Mapping of EUROCAT Congenital Anomaly Subgroups to MedDRA®

To enable identification of corresponding medication–CA pairs in VigiBase, the 61 EUROCAT anomaly subgroups included in the EUROmediCAT analysis were mapped to MedDRA® terms. The closest match between the EUROCAT subgroup and a MedDRA® PT was mapped by hand by a UMC coding specialist, on the advice of a clinical geneticist. The PT refers to a single medical concept and is the level that is used in routine signal detection [39, 40]. Some EUROCAT subgroups mapped to more than one MedDRA® term, e.g. "Aortic valve atresia/stenosis" was mapped to "Aortic valve atresia" and "Congenital aortic valve stenosis". To define the aggregated EUROCAT subgroup "Congenital heart defects", nine HLTs were grouped. Supplementary Table 4 (see the electronic supplementary material) includes a listing of the mapped terms.

2.2.4 Statistical Methods in VigiBase

Signals detected in the EUROmediCAT analysis were matched to medication–CA pairs in the VigiBase-CA dataset using the mapped MedDRA® terms and the corresponding ATC codes in WHODrug. Signals with ATC-4 codes were matched to the subordinated individual substances in the VigiBase-CA dataset as this level of specificity is used in routine detection of signals in VigiBase. To analyse statistical reporting patterns of medication–CA pairs in VigiBase, PRRs were computed.

It is acknowledged that medication–adverse event pairs with a very strong association (for example, known teratogens) may hide patterns for other medications with the event in question or other events with the medication in question. To uncover such patterns, a simple unmasking algorithm

was used [41], where influential outliers were defined as medication–CA pairs which, upon removal, decreased the expected value of the anomaly or medication by more than 10%. Reports containing influential outliers were then excluded when calculating unmasked PRRs. Medication–CA pairs were considered disproportionately over-reported in VigiBase if they had at least three reports and either (1) a PRR_{025} (the lower limit of the 95% two-sided CI) > 1 or (2) an unmasked PRR_{005} (the lower limit of the 99% two-sided CI) > 1. A stricter CI was used for unmasked PRRs to minimise the number of spurious associations [41].

2.2.5 VigiBase Case Series Review

For each matched medication–CA pair, the case series was reviewed in the context of different clinical aspects to classify whether it was reasonably supportive of the EUROmediCAT findings or inconclusive. Individual case reports were analysed in detail, where the timing of the gestational exposure and the underlying condition of the mother as well as any co-medications used during the pregnancy were the most important factors considered. Other factors, such as the demographic and lifestyle characteristics of the mother and biological plausibility, were also considered.

2.3 Evaluating EUROmediCAT Signals in Literature and Product Labelling

Signals detected in the EUROmediCAT analysis were cross-checked with results from the previous EUROmediCAT signal detection analysis [18, 19] as well as studies performed on specific medication groups (anti-epileptics [30, 42–44], anti-asthmatic [45], anti-diabetic [46] and anti-depressants [47]), since the data analysed in this study include data used in these previous analyses. A literature review was performed for each association not previously investigated, to determine if there were previous reports of human teratogenicity for these new associations. This was done by searching PubMed and the Developmental and Reproductive Toxicology Database (DART) using the specific medication, ATC terms and the name of the medication group combined with search terms for teratogen and anomaly. To incorporate established knowledge on risks of in utero exposure, the regulatory product information from the United States and Europe were also consulted [48, 49]. Results of the literature search and product labelling reviews were considered together and summarised with a combined rating, by consensus of five authors (JKM, AC, LS, IÖ and KS):

1. Well established human teratogenicity
2. Some evidence of human teratogenicity in the literature/regulatory labelling

3. Limited or no evidence of human teratogenicity in the literature/regulatory labelling

2.4 Evidence Synthesis and Rating of Evaluated Signals

EUROmediCAT and VigiBase results were further considered in the light of the literature and product labelling ratings, in order to synthesise these with the available level of quantitative and qualitative evidence from both databases, and make a recommendation as to which signals warrant further investigation in independent studies. This evaluation was made for each signal using the following categories

- Non-specific medications
- Maternal disease rather than medication
- Established teratogen
- Previously recommended for further investigation in EUROmediCAT studies
- Insufficient evidence for recommending further investigation
- Signal recommended for further investigation

These final recommendations took into account the statistical reports of disproportionality from both databases, information from the EUROmediCAT cases including the accuracy of the timing of medication exposure, the geographical distribution of cases and the presence of concomitant medications, anomalies or maternal conditions and information from the case series review in VigiBase, as well as considering the strength of findings in the literature and product labelling. Cases were individually checked with EUROmediCAT registries for all signals recommended for further investigation, to confirm the CA, medication code and timing of exposure. Established teratogens were not considered requiring further review.

3 Results

3.1 Description of EUROmediCAT and VigiBase-CA Datasets

Table 1 summarises the EUROmediCAT data available for analysis according to registry. After excluding foetuses with medication exposures not stated as being in the first trimester, there were 21,636 cases in the data with 32,619 medication exposures. This is an additional 6692 cases and 9508 medication exposures compared to that analysed previously [18]. In total, there were 563 ATC-5 medications and 293 ATC-4 medications. Data loss was highest for registries where it was not possible to verify when the reported medications had been taken, as discussed previously [18]. The

distributions of type of anomaly were similar for those pregnancies excluded due to unknown timing and those included, suggesting that cases remaining in the dataset for these registries should not be prone to selection biases in this respect.

The VigiBase-CA dataset included 45,749 reports from 82 countries. European countries accounted for 27% of the reports, while the United States contributed more than half of the reports (58%). The reports represented 165,121 medication exposures with 2892 unique substances characterised as suspect or interacting. The type of report was given in 98% of the cases; most were spontaneously reported (84%), a small proportion was from studies (9.1%), and the remaining reports were from other sources. The type of reporter was stated in 98% of the cases; physician (42%), consumer or non-health professional (22%), other health professional (18%), lawyer (10%), pharmacist (4.3%), and other types of reporters (3.7%).

The numbers of cases in each of the anomaly subgroups that were examined for medication associations is displayed in Supplementary Table 1 (see the electronic supplementary material). In the EUROmediCAT dataset, 17.2% ($n = 3721$) of cases had an anomaly that was not one of the 61 specified EUROCAT subgroups, compared to 54.3% ($n = 24,818$) of reports in the VigiBase-CA dataset. These cases were included as an "anomaly comparison group" for each dataset. In the EUROmediCAT dataset, a quarter of cases were exposed to at least one "nervous system" medication (40% of cases in the VigiBase-CA dataset), with almost as many being exposed to at least one medication in the ATC group "Genito-urinary system medication and sex hormones" (8% of cases in the VigiBase dataset) (Supplementary Table 5). The distribution of the number of medication exposures per case for both datasets is shown in Supplementary Figure 1. In EUROmediCAT, 66% of cases had only one reported medication exposure, whereas in VigiBase, 7% of reports included only one reported medication characterised as suspected or interacting.

3.2 EUROmediCAT Signal Detection and Selection Process

Figure 1 describes the number of medication–CA combinations and reasons for exclusions at each stage of the signal detection and selection process. Following Fisher's test and the double FDR procedure, there were 139 statistically significant signals with at least three exposed cases. The selection process then excluded a further 90 medication–CA combinations. Finally, only those signals retaining statistical significance after adjustment for registry were retained, resulting in 49 signals of independent medication–CA associations that were investigated in more detail by EUROmediCAT and in the VigiBase-CA dataset.

Table 1 Description of EUROmediCAT signal detection dataset

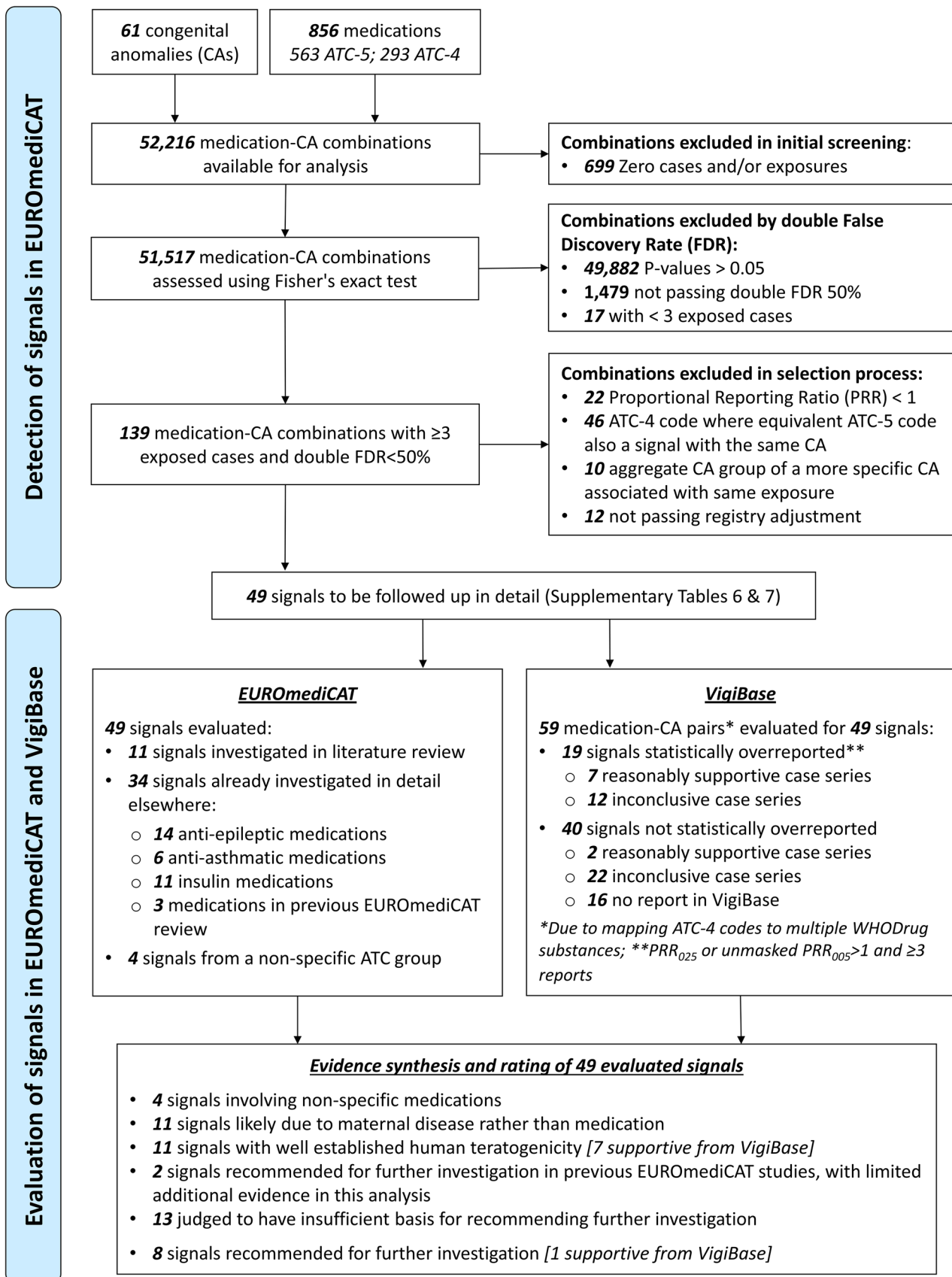| EUROCAT Registry	Birth years included	Additional years of data since 1st signal detection analysis	Foetuses with CAs and at least one valid exposure	Foetuses with CAs following data cleaning by exposure timing[a]	Data loss by data cleaning[a] (%)	N (%) new cases[b]	Total eligible ATC coded exposures[c]	Average ATC medication exposures per pregnancy[c]
Belgium, Antwerp	1995–2015	From 2012	504	479	5	110 (23.0%)	666	1.4
Croatia, Zagreb	1995–2013	From 2011	233	217	7	40 (18.4%)	853	1.2
Denmark, Odense	1995–2013	From 2012	302	302	0	61 (20.2%)	400	1.5
France, Paris	2001–2015	From 2012	952	952	0	294 (30.9%)	4000	1.4
France, Isle de Reunion	2005–2014	All (new)	275	274	< 1	274 (100%)	5495	1.4
Germany, Mainz	1996–2014	From 2012	320	317	1	73 (23.0%)	376	1.2
Germany, Saxony Anhalt	2000–2015	All (new)	1221	1214	< 1	1214 (100%)	364	1.4
Ireland, Cork and Kerry	1996–2012	From 2010	292	290	1	36 (12.4%)	788	1.4
Ireland, South-East Ireland	2007–2014	All (new)	67	56	16	56 (100%)	4896	1.6
Italy, Emilia Romagna[d]	1995–2015	From 2012	2566	2560	< 1	216 (8.4%)	447	1.6
Italy, Tuscany	1995–2015	From 2012	1345	1226	9	192 (15.7%)	1331	1.4
Malta	1996–2015	From 2012	519	517	< 1	180 (34.8%)	3073	1.5
Netherlands, Northern	1995–2015	From 2012	2864	2731	5	423 (15.5%)	1627	1.8
Norway	2005–2010	None	3051	3051	0	0 (0%)	83	1.8
Poland (excl. Weilkopolska)	1999–2011	From 2011	13,683	2463	82	248 (10.1%)	1629	1.3
Poland, Wielkopolska	1999–2015	From 2011	3854	542	86	110 (20.3%)	435	1.3
Spain, Basque Country	2005–2014	All (new)	634	578	9	578 (100%)	907	1.5
Spain, Valencian Region	2007–2015	All (new)	1095	618	44	618 (100%)	688	1.5
Switzerland, Vaud	1995–2015	From 2012	472	453	4	136 (30.0%)	3594	1.6
UK, Wales	1998–2015	From 2012	2481	2480	< 1	391 (15.8%)	716	1.5
Ukraine	2005–2015	All (new)	320	316	1	316 (100%)	251	1.4
Total	1995–2015		37,050	21,636	42	5566 (25.7%)	32,619	1.5

ATC Anatomical Therapeutic Chemical, *CA* congenital anomaly

[a]Exclusion of CA registrations with exposures only to medication of unknown timing, folic acid, minerals and/or vitamins, those with ATC codes with less than 5 digits and topical medications

[b]Compared to the previous EUROmediCAT signal detection analysis by Luteijn et al[18]

[c]Exposure to medications included in signal detection analysis, i.e. ATC coded medications with at least 3 exposures across the dataset

[d]During the period 1995–2004, the Emilia Romagna database had space for only 5 medications to be recorded. Terminations of pregnancy for foetal anomalies were excluded from the Emilia Romagna registry, as information on medications is only available for live and still births

Detection of signals in EUROmediCAT

61 congenital anomalies (CAs)

856 medications
563 ATC-5; 293 ATC-4

52,216 medication-CA combinations available for analysis

Combinations excluded in initial screening:
• **699** Zero cases and/or exposures

51,517 medication-CA combinations assessed using Fisher's exact test

Combinations excluded by double False Discovery Rate (FDR):
• **49,882** P-values > 0.05
• **1,479** not passing double FDR 50%
• **17** with < 3 exposed cases

139 medication-CA combinations with ≥3 exposed cases and double FDR<50%

Combinations excluded in selection process:
• **22** Proportional Reporting Ratio (PRR) < 1
• **46** ATC-4 code where equivalent ATC-5 code also a signal with the same CA
• **10** aggregate CA group of a more specific CA associated with same exposure
• **12** not passing registry adjustment

49 signals to be followed up in detail (Supplementary Tables 6 & 7)

Evaluation of signals in EUROmediCAT and VigiBase

EUROmediCAT

49 signals evaluated:
• **11** signals investigated in literature review
• **34** signals already investigated in detail elsewhere:
  ○ **14** anti-epileptic medications
  ○ **6** anti-asthmatic medications
  ○ **11** insulin medications
  ○ **3** medications in previous EUROmediCAT review
• **4** signals from a non-specific ATC group

VigiBase

59 medication-CA pairs* evaluated for **49** signals:
• **19** signals statistically overreported**
  ○ **7** reasonably supportive case series
  ○ **12** inconclusive case series
• **40** signals not statistically overreported
  ○ **2** reasonably supportive case series
  ○ **22** inconclusive case series
  ○ **16** no report in VigiBase

*Due to mapping ATC-4 codes to multiple WHODrug substances; **PRR_{025} or unmasked PRR_{005}>1 and ≥3 reports*

Evidence synthesis and rating of 49 evaluated signals

• **4** signals involving non-specific medications
• **11** signals likely due to maternal disease rather than medication
• **11** signals with well established human teratogenicity [7 supportive from VigiBase]
• **2** signals recommended for further investigation in previous EUROmediCAT studies, with limited additional evidence in this analysis
• **13** judged to have insufficient basis for recommending further investigation
• **8** signals recommended for further investigation [1 supportive from VigiBase]

◄**Figure 1.** Signal detection and selection process in EUROmediCAT and follow-up of associations in VigiBase. *ATC* Anatomical Therapeutic Chemical, *CA* congenital anomaly, *FDR* false discovery rate, *PRR* proportional reporting ratio

3.3 Signal Evaluation in EUROmediCAT and VigiBase

Figure 1 shows that of the 49 signals resulting from the EUROmediCAT signal detection process, four referred to non-specific medications (and therefore not investigated further) and 34 had already been considered in detail elsewhere (anti-asthmatic, anti-epileptic or insulin medications, or already investigated in the previous EUROmediCAT review [19]); the remaining 11 signals were investigated in a new literature review to determine if there was any published information about their teratogenicity. Mapping ATC-4 exposures in the EUROmediCAT data to the subordinated substances in VigiBase resulted in 59 medication–CA pairs being evaluated in the VigiBase data.

Supplementary Table 6 (see the electronic supplementary material) presents details of the 49 medication–CA associations from signal detection analysis in EUROmediCAT and the corresponding 59 medication–CA pairs in VigiBase. Results presented include the number of cases for each medication–CA association and the related PRR and 95% CI for each database. Concurrent medication exposures listed in the EUROmediCAT database are also noted, and for VigiBase, a summary of the case series review is presented. Of the 59 medication–CA pairs investigated in the VigiBase-CA dataset, 16 had a $PRR_{025} > 1$ and a case series including at least three reports. One of these (valproic acid and spina bifida) was also identified as an influential outlier. The removal of this and other influential outliers identified by the unmasking algorithm uncovered three additional pairs with $PRR_{005} > 1$ and at least three reports. Of these, in total, 19 disproportionately overreported pairs, the case series was considered reasonably supportive of the EUROmediCAT finding in seven and inconclusive in 12. Two additional case series were considered reasonably supportive but did not reach any statistical significance. The remaining 38 case series were either inconclusive (22) or had no reports in VigiBase (16). The main reasons for an inconclusive outcome of the case series review were sparsely documented cases, limiting the possibility for a proper evaluation, and the identification of alternative explanations for the anomaly, such as concurrent teratogenic medications. See Fig. 1 for a summary of these results.

3.4 Rating of Literature and Product Labelling Review, and Overall Evaluation of Signals

Supplementary Table 7 (see the electronic supplementary material) presents the results of the literature search and product labelling reviews for each of the 49 signals, including a rating to summarise the strength of existing evidence for human teratogenicity; 11 were of well-established human teratogenicity in the literature/regulatory labelling, nine had some evidence, and 25 had limited or no evidence, and four non-specific medication groups were not considered in detail. The final column of Supplementary Table 7 presents the overall evaluation of both the existing evidence ratings and the EUROmediCAT and VigiBase data; of the 49 signals, 41 were judged not to require further follow-up for the following reasons: (1) four were for non-specific medication groups, (2) 11 were likely to be due to maternal disease rather than medication, (3) 11 referred to well-established human teratogenicity in both the literature and existing labelling, (4) two had been recommended for further investigation in previous EUROmediCAT studies, with limited additional evidence in this analysis, and (5) 13 were judged to have insufficient basis for recommending further investigation (Fig. 1). The full details are given in Supplementary Tables 6 and 7.

Details of the eight signals noted as warranting further investigation in future studies are presented in Tables 2 and 3, and are considered in more detail in the "Discussion" section. These signals included five different medications in combination with eight different anomalies: pregnen (4) derivatives with limb reduction; nitrofuran derivatives with cleft palate and patent ductus arteriosus; salicylic acid and derivatives with atresia or stenosis of other parts of the small intestine and tetralogy of Fallot; carbamazepine with atrioventricular septal defect and severe CHD; selective beta-2-adrenoreceptor agonists with posterior urethral valve and/or prune belly (Table 2). Of these eight signals recommended for further investigation, six had some evidence of human teratogenicity in the literature/labelling and two had limited evidence. One of these was statistically overreported in VigiBase but with inconclusive case series, and one was concluded to be reasonably supportive following manual case series review, although not statistically overreported. CA cases, medication codes and timing of exposure were confirmed with EUROmediCAT registries for all signals recommended for further investigation, with the exception of one fewer case of limb reduction defect (an antenatal finding of short femurs that was found to be normal postnatally), meaning that there were 59 cases for the signal of pregnen (4) derivatives with limb reduction.

Table 2 Details of signal detection analysis in EUROmediCAT and evaluation of signals in VigiBase for eight medication-CA associations recommended as warranting further investigation

EUROmediCAT analysis		CA	EUROmediCAT results				VigiBase results			
ATC code Chemical sub-group/substance name			*N* cases [total *N* with medication exposure; total *N* with anomaly] *N* per registry	PRR[a] (95% CI) adjusted for registry	Concurrent medication exposures (*n*)	Concurrent anomalies (*n*)	WHO drug substance name	*N* cases	PRR[a] (95% CI)	Case series review
G03DA Pregnen (4) derivatives[b]		Limb reduction	60[e] [1624; 590] Cases in 13 registries: Poland (14), Tuscany (13), Wielkopolska (7), Norway (5), N Netherlands (4), Emilia Romagna (4), Antwerp (3), Wales (3), Cork and Kerry (2), Ukraine (2), Vaud (1), Saxony Anhalt (1), Valencian Region (1)	1.31 (1.00–1.71)	NONE (28) N02BA01 (6), N02BE01 (4), G03DB01 (4), G03GA08 (3), G03CA03 (2), C02AB01 (2), H03AA01 (2), B01AB05 (2) +30 further medications with 1 exposure	NONE (14) Vascular disruption (29), other limb defects (19), CHDs (9), digestive system (4), clefts (6), hydrocephalus (5), abdominal wall defects (4), NTDs (2), urinary (2), congenital constriction bands/amniotic band (2), genital (1)	Progesterone	1	1.65 (0.23–11.61)	*Inconclusive* Sparse doc
J01XE Nitrofurantoin derivatives		Cleft palate	20 [312; 620] Cases in 5 registries: Poland (11), N Netherlands (4), Norway (2), Wielkopolska (2), Antwerp (1)	1.76 (1.14–2.73)	NONE (10) J01CA04 (3), N02BE01 (2), J01CA08 (2) +7 further medications with 1 exposure	NONE (14) CHDs (5), limb defects (2), anorectal atresia and stenosis (1), hypospadia (1), congenital skin disorders (1)	Nitrofurantoin	5	2.72 (1.17–6.34)	*Inconclusive* Sparse doc cases with no specified time of exposure or polypharmacy
		Patent ductus arteriosus as only CHD in term infants	13 [312; 314] Cases in 4 registries: Norway (7), Poland (3), Wielkopolska (2), Vaud (1)	2.41 (1.40–4.17)	NONE (5) J01CA08 (3) +10 further medications with 1 exposure	NONE (12) Cleft palate (1)		6	2.01 (0.93–4.31)	*Inconclusive* Non-eligible reports (all but one did not meet the case definition due to prematurity or other CHDs)

Table 2 (continued)

EUROmediCAT analysis	CA	EUROmediCAT results				VigiBase results			
ATC code Chemical sub-group/substance name		N cases [total N with medication exposure; total N with anomaly] N per registry	PRR[a] (95% CI) adjusted for registry	Concurrent medication exposures (n)	Concurrent anomalies (n)	WHO drug substance name	N cases	PRR[a] (95% CI)	Case series review
N02BA Salicylic acid and derivatives[b]	Atresia or stenosis of other parts of small intestine	9 [866; 96] Cases in 4 registries: Tuscany (2), Emilia Romagna (2), Isle de Reunion (1), Paris (1)	2.09 (1.04–4.20)	NONE (3) H02AB06 (2), H03AA01 (2), C08CA05 (2) +8 further medications with 1 exposure	NONE (4) Vascular disruption (5)	-	0	-	-
	Tetralogy of Fallot	21 [893; 304] Cases in 6 registries: Emilia Romagna (4), Wales (3), Ukraine (1), Tuscany (1), Saxony Anhalt (1), Paris (1)	1.57 (1.01–2.46)	NONE (10) B01AB05 (3), C02AB01 (2),G03DA04 (2), A10BA02 (2) +17 further medications with 1 exposure	NONE (17) Other CHD (3), oesophageal atresia (1), polydactyly (1)	Acetylsalicylic acid	2	0.25 (0.06–1.00)	*Inconclusive* Sparse doc
N03AF01 Carbamazepine	Atrioventricular septal defect	7 [197; 202] Cases in 4 registries: Wales (3), Poland (2), Tuscany (1), Antwerp (1)	3.76 (1.78–7.93)	NONE (5) R03AK06 (1), N03AA02 (1)	NONE (3) Other CHD (2), cleft palate (1), hypospadia (1), syndactyly (1)	Carbamazepine	1	0.35 (0.05–2.52)	*Inconclusive* One case, co-medicated with topiramate

Table 2 (continued)

EUROmediCAT analysis		EUROmediCAT results				VigiBase results			Case series review
ATC code Chemical sub-group/substance name[b]	CA	N cases [total N with medication exposure; total N with anomaly] N per registry	PRR[a] (95% CI) adjusted for registry	Concurrent medication exposures (n)	Concurrent anomalies (n)	WHO drug substance name	N cases	PRR[a] (95% CI)	
	Severe CHD	30 [203; 1871] Cases in 6 registries: Poland (9), Wales (6), Tuscany (3), N Netherlands (3), Norway (2), Cork and Kerry (2)	1.67 (1.20–2.34)	NONE (24) +10 medications with 1 exposure	NONE (21) Situs inversus (3), other CHD (2), limb defects (2) hydrocephalus (2), hypospadia (2), lateral anomalies (2), anophthalmos (1), choanal atresia (1), cleft palate (1), congenital hydronephrosis (1)	-	29	0.66 (0.46–0.95)	*Reasonably supportive* One third of cases report monotherapy or co-medication with drugs with no known teratogenicity in first trimester and few other obvious alternative explanations. One third with monotherapy but sparse doc cases. One third co-medication with valproic acid or topiramate. Reporting spread over time and countries
R03AC Selective beta-2-adrenoreceptor agonists[b]	Posterior urethral valve and/or prune belly	14 [1183; 112] Cases in 6 registries: Wales (4), N Netherlands (2), Odense (2), Malta (1), Norway (1), Paris (1)	1.83 (1.02–3.28)	NONE(4) R03DA01(2), R03AK06(2) +16 further medications with 1 exposure	NONE(6) Congenital hydronephrosis (6), hip dislocation and/or dysplasia (1), congenital skin disorders (1)	-	0	-	-

ATC Anatomical Therapeutic Chemical, *CA* congenital anomaly, *CHD* congenital heart defect, *CI* confidence interval, *doc* documented, *NTD* neural tube defect, *PRR* proportional reporting ratio, *WHO* World Health Organization

[a]PRR: The proportion of exposures to each specific medication in cases with a specific anomaly, compared to the proportion of exposures to that medication in the anomaly comparison group

[b]Medication exposures at ATC-4 include substances with multiple ATC-5 codes: G03DA includes medroxyprogesterone (G03DA02 and G03AC06), N03BA includes acetylsalicylic acid (N02BA01, B01AC06 and A01AD05), and R03AC includes salbutamol (R03AC02 and R03CC02)

[c]Following individual case checks with registries, 1 case was reclassified as not having limb reduction defect; hence, whilst the analysis included $n = 60$, the actual number of cases for this signal is $n = 59$

Table 3. Literature and product labelling review, evidence synthesis from EUROmediCAT and VigiBase results, and overall evaluation of eight signals of medication–CA associations recommended as warranting further investigation

ATC code Chemical subgroup/substance	CA	Information from previous EUROmediCAT studies and literature review	Product labelling information[a]	Literature/regulatory labelling, and reason signal considered to warrant further investigation
G03DA Pregnen (4) derivatives	Limb reduction	In previous EUROmediCAT review [19]; previous studies have found a significant association between "sex hormones" and certain CAs. However, poor methodology and a lack of consistent results have resulted in the conclusion that there is no evidence that sex hormones produced nongenital organ teratogenesis [50]	"Data on a large number of exposed pregnancies indicate no adverse effects of progesterone on the foetus." [48] "There is limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy." (progesterone) [48]	Limited evidence of human teratogenicity in the literature/regulatory labelling (*), and only 1 sparsely documented case in VigiBase. However, there was an increased number of cases compared to the previous EUROmediCAT signal detection analysis (59 vs 5), and with a different CA subgroup to that analysed previously (limb reduction vs complete absence of a limb[b]). Cases were from 13 registries, of which 28 had no other medications recorded and 14 had no other anomalies recorded. This warrants further investigation in other studies
J01XE Nitrofuran derivatives	Cleft palate PDA as only CHD in term infants	Case–control studies have reported increased risk of clefts, but this was based on self-reports after birth [6, 57, 58] and cohort studies have lacked the power to confirm this [59–61]. ACOG opinion was that the evidence regarding an association of nitrofuran class of antibiotics and birth defects was mixed [62]. An association of cardiovascular malformations and nitrofuran derivatives has not been reported as consistently as that for clefts	"Extensive clinical use since 1952, suitability in pregnancy has been well documented." (nitrofurantoin) [48]. Animal study 68 x human dose observed growth retardation and a low incidence of minor and common malformations. No adequate and well-controlled studies in pregnant women (nitrofurantoin) [49]	Some evidence of human teratogenicity in the literature/regulatory labelling for both signals (**). Results from VigiBase inconclusive for both signals. Sufficient cases with mainly isolated anomalies and specific medication exposures in EUROmediCAT data to warrant further investigations in independent studies. Concern that 50% of cases are from one registry (Poland)

Table 3. (continued)

ATC code Chemical subgroup/substance	CA	Information from previous EUROmediCAT studies and literature review	Product labelling information[a]	Literature/regulatory labelling, and reason signal considered to warrant further investigation
N02BA Salicylic acid and derivatives	Atresia or stenosis of other parts of small intestine Tetralogy of Fallot	An association with gastroschisis has been recorded [7, 51–53, 63], but no association with atresia or stenosis of other parts of small intestine has been found. One study noted a non-significant association between conal malformations of the heart and acetylsalicylic acid, 8.5% vs 7.8% [64]. Other studies have not found an increased association [7, 53]	"Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy." (acetylsalicylic acid) [48]	Some evidence of human teratogenicity in the literature/regulatory labelling for both signals (**). Very few cases in VigiBase. Signals with reasonable numbers of cases in the current EUROmediCAT analysis (9 atresia or stenosis cases from 4 registries, 4 isolated anomalies; 21 tetralogy of Fallot cases from 6 registries, 17 isolated), and as signals have been previously observed for this medication group with anomalies in different organ system classes. This warrants further investigation in other studies
N03AF01 Carbamazepine	Atrioventricular septal defect Severe CHD	Carbamazepine previously investigated in EUROmediCAT [65], and increased risk of spina bifida observed in other studies confirmed. Exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect. Associations with CHDs have not been noted in other studies	"Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. There have also been reports that associate with developmental disorders and congenital anomalies (e.g., craniofacial defects, cardiovascular malformations and anomalies involving various body systems)." [49]	Some evidence of human teratogenicity in the literature/regulatory labelling for both signals (**). Although not statistically overreported, the signal for severe CHD had a reasonably supportive case series in VigiBase. This medication has been reported in association with spina bifida, with tentative associations of an increased risk of some CHDs in previous EUROmediCAT analyses. Along with the number of cases (mainly isolated anomalies and carbamazepine as the only reported medication) in EUROmediCAT, these signals warrant further investigation in other studies

Table 3. (continued)

ATC code / Chemical subgroup/substance	CA	Information from previous EUROmediCAT studies and literature review	Product labelling information[a]	Literature/regulatory labelling, and reason signal considered to warrant further investigation
R03AC / Selective beta-2-adrenoreceptor agonists	Posterior urethral valve and/or prune belly	Inhaled beta-2-agonists investigated in EUROmediCAT showed increased odds for cleft palate, which was previously interpreted as being of concern, but with no association for posterior urethral valve and/or prune belly [66]	"A moderate amount of clinical data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of salmeterol." [48] "Safety in pregnant women has not been established. Rare reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received." [48] "Although no teratogenic effects have been observed in animals or in patients, [terbutaline] should only be administered with caution during the first trimester of pregancy." [48]	Limited evidence of human teratogenicity in the literature/regulatory labelling (*). No cases present in VigiBase. These medications have been previously shown an association with other types of anomaly, but have not been linked to posterior urethral valve and/or prune belly. Combined with the number of EUROmediCAT cases (14 from 6 registries, 6 isolated anomalies), this warrants further investigation in other studies

ATC Anatomical Therapeutic Chemical, *CA* congenital anomaly, *CHD* congenital heart defect, *PDA* patent ductus arteriosus

[a]For ATC-4 drug groups this refers to labels for the corresponding substances for which there were reports in VigiBase

[b]Due to changes in EUROCAT coding, "complete absence of a limb" is no longer a separate EUROCAT anomaly subgroup

4 Discussion

Signal detection analysis using EUROmediCAT data resulted in 49 signals of medication–CA associations. After using VigiBase as a complementary source of reference and also conducting a review of existing literature and product labelling, eight signals were recommended for further investigation in independent studies before drawing conclusions regarding their teratogenicity.

The first EUROmediCAT signal detection analysis found a signal for pregnen (4) derivatives with the EURO-CAT anomaly subgroup complete absence of a limb, but no signal for limb reduction defects [18, 19]. However, in this study there was a signal for pregnen (4) derivatives and limb reduction with a large number of cases in the EUROmediCAT analysis dataset but only one case present in VigiBase (Table 2). Cases with complete absence of a limb are included in the limb reduction defects subgroup; however. this is no longer a specific subgroup in the updated EUROCAT coding guide and was therefore not analysed separately in this study [26]. Studies have examined the association between "sex hormones" and certain congenital anomalies; however, such studies have often had conflicting results and their methodology has been criticised [19, 50] (Table 3). We believe the occurrence of 59 exposed cases in the current EUROmediCAT study warrants further investigation in other studies. There were two signals for nitrofuran derivatives with cleft palate and with patent ductus arteriosus as the only CHD in term infants ($\geq$ 37 weeks), for which there have been previous indications in the literature, but often with no specific conclusions drawn due to small samples and poor methodology (Table 3). Results from VigiBase were inconclusive for these two signals: although cleft palate was statistically overreported, there was a small number of cases (five and six, respectively) with unspecified exposure timing, polypharmacy or not meeting the EUROmediCAT case definition of term pregnancy for patent ductus arteriosus with no other CHDs. However, we believe these signals have sufficient cases in EUROmediCAT data to warrant further investigations in independent studies. For the remaining five signals noted as warranting further investigation, specific anomalies have been identified previously as being associated with the medication, but the EUROmediCAT results here indicate that other anomalies may also have increased risks. Firstly, salicylic acid and derivatives have previously been linked to an increased risk of gastroschisis [51–53]; however, in this study, we found a signal for the same medication with two anomalies in different organ system classes (atresia or stenosis of other parts of the small intestine, tetralogy of Fallot). Next, there have been signals for carbamazepine with both atrioventricular septal defect and the more general group of severe CHDs; carbamazepine has

been reported in association with spina bifida [43], and in this review of cohort studies from 1995 to 2005, an exploratory analysis also found a higher (than expected by chance) reported proportion of two severe CHDs associated with carbamazepine use: single ventricle and atrioventricular septal defect. However, limited conclusions were drawn due to the possibility of chance findings associated with multiple comparisons; hence, the current study adds more evidence to this initial finding. Although not statistically overreported, there was also a reasonably supportive case series for carbamazepine and severe CHD in VigiBase. Finally, whilst selective beta-2-adrenoreceptor agonists have previously been shown to have associations with other types of anomaly, they have not previously been linked to posterior urethral valve and/or prune belly. We recommend these associations be investigated further in independent studies, which may provide aetiological insights into their potential teratogenicity.

4.1 Differences Between the EUROmediCAT and VigiBase Databases

When considering the results of this study it is important to reflect on differences between the EUROmediCAT and VigiBase databases, and the specific datasets used for these analyses. The key difference between the two databases is that EUROmediCAT is population-based registry data and VigiBase is spontaneous reporting data. As such, EUROmediCAT data on medication exposures is often collected from maternal medical notes recorded before the CA is known and is unlikely to contain over-the-counter (OTC) medications, whereas VigiBase concerns the spontaneous reporting of adverse events collected retrospectively and includes both prescribed and OTC medications. VigiBase data may be more prone to under-reporting and other bias in reporting, for example, following publicity or regulatory action on specific medications or anomalies [54, 55], which can impact statistical analyses. Extreme reporting rates of certain associations can cause masking of true signals, which is why an unmasking algorithm was applied to the VigiBase data. This approach revealed three additional signals with positive PRRs that were otherwise masked by other reports. Another difference between the two databases is the level of available detail. EUROmediCAT includes only major malformations, while the VigiBase-CA dataset was not restricted to major malformations but included some minor malformations as well as congenital disorders not classified as malformations. Anomalies in EUROmediCAT in general seemed more granularly coded than anomalies in VigiBase; hence, some lower report counts in VigiBase could be due to those anomalies having been coded to a less specific term, and therefore are not being captured in the case series. The potential differences in classifying anomalies needed to be considered when assessing the consistency of evidence

from both data sources. Conversely, specific information on medication substances is generally available in VigiBase while not always available in EUROmediCAT. It is difficult to comprehensively assess a signal based only on ATC-4 level information; however, the inclusion of ATC-4 codes in EUROmediCAT signal detection methodology is done in order to be as inclusive as possible. We also emphasise that the EUROmediCAT approach to signal detection is one of hypothesis generating, with further, more specific, investigations being required.

The geographical coverage of the two databases also differs, with EUROmediCAT covering 15 European countries compared to VigiBase, which has worldwide coverage. The VigiBase-CA dataset used in this study included reports from 82 countries, with 27% of reports coming from European countries. As EUROmediCAT covers around 10% of European births over this period, the overlap between data sources is likely to be less than 3% of cases. VigiBase data thus represent a more heterogeneous population encompassing broader variations, e.g. in medication use, medical practice, and at-risk subpopulations.

The number of cases often differed considerably between EUROmediCAT and VigiBase. For most associations, VigiBase presented fewer cases; however, for ten out of the 11 associations with well-established human teratogenicity, VigiBase had more reports. It should be emphasised that spontaneous reporting systems in general are based on the reporting of *suspected* adverse drug reactions, where there is at least a reasonable possibility of a causal relationship between a medication and an adverse event. Thus, it could be speculated that medication–CA associations may be less prone to be suspected and reported to such systems if the underlying disease, and not the medication, is known to be associated with the anomaly (e.g. insulin and cardiac anomalies), or if the medication is commonly used during pregnancy with no known teratogenicity (e.g. levothyroxine). Such medications might also, when reported, have been classified as *concomitant* on the reports in VigiBase and, hence, are not captured in this study where the search criteria were set to retrieve cases with medications characterised as *suspected* or *interacting*. Only 49 selected EUROmediCAT associations were assessed, however, so the low reporting rates for many medication–CA pairs in VigiBase might not be representative of potential CA-related harm in this database; other potential and known teratogens that were not assessed here may also be present.

4.2 Strengths and Limitations of this Study

In the study of rare diseases it is important to have large databases covering millions of births in order to have the case numbers and statistical power to conduct meaningful analyses. In this study, we utilised data from two large,

international databases. The EUROmediCAT database contains detailed information on the coding of all congenital anomalies as well as information on medications taken during the first trimester of pregnancy. A particular strength of EUROmediCAT is that the medications are known to occur in the first trimester. In VigiBase data, the timing of pregnancy exposure is not always captured in the structured format, so statistical measures may include reports with exposures outside of the first trimester, although exposure timing can also be found as free-text information or interpreted from reported dates, which was considered for each signal in the manual case review. Another limitation of this study is that there was often a lack of additional information per report/case in both databases for key associations of interest. On the other hand, when narrative information was available in VigiBase reports, this was often very informative and useful in the evaluation. Signal detection analysis in EUROmediCAT only considers individual medications, although available information regarding polytherapy and co-medications were considered for all signals investigated in further detail in both databases. Regarding folic acid usage, this is not accurately reported in EUROmediCAT, since it is generally an OTC medication, and is not routinely prescribed in the majority of European countries. We were therefore not able to perform a reliable sensitivity analysis adjusting for folic acid in the analysis of NTDs.

4.3 Value of Including VigiBase in this Type of Study and Future Work

Review of VigiBase data often weakened the EUROmediCAT findings, primarily due to the identification of confounding factors and sparse reporting/absence of reports. However, VigiBase did provide supportive information for the majority of signals with well-established teratogenicity and, although supportive of only one of the eight signals warranting further investigation, also helped inform decisions regarding selection of these signals.

In this study, the EUROmediCAT registry was used to detect signals, while VigiBase was used only secondarily to explore the already identified signals. It should be emphasised that UMC did not do a full signal screening, which would have resulted in another output of signals. The EUROmediCAT method for signal detection differs from UMC's standard signal screening methodology that considers both quantitative and qualitative aspects [21]. Future work could be to develop a screening method tailored to detect signals of congenital anomalies in VigiBase and then use EUROmediCAT as a reference source in the assessment.

We performed this second signal detection due to additional data and new improved methodology. However, since the first EUROmediCAT signal detection paper in 2016, the signals recommended previously as warranting further

evaluation have not, to the best of our knowledge, been considered in more detail. Therefore, there is now a need to develop a process to stimulate the further evaluation of the signals identified here, which will include considering how frequently signal detection in the EUROmediCAT database should be performed.

5 Conclusions

EUROmediCAT data should continue to be used in the future for signal detection, accompanied by additional information from VigiBase and review of the existing literature to prioritise signals for further independent evaluation. A system for evaluating these signals needs to be initiated.

Declarations

Conflict of interest As of June 2020, Kristina Star is a full-time employee of AstraZeneca. However, all of her contributions to this work were made prior to the time of departure, as part of her employment at Uppsala Monitoring Centre. All other authors declare that they have no conflict of interest.

Ethics Approval Not applicable.

Consent to participate All data in EUROmediCAT and VigiBase are anonymised; therefore, patient informed consent for this particular study was not required.

Consent for publication Not applicable.

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 http://euromedicat.eu/currentresearchanddata/howtoproposeorcommissionspecificstudies. The VigiBase datasets generated and analysed during the current study are not publicly available due to agreements between contributors of data to the database used (VigiBase) and the custodian of this database. National centres (mainly national drug regulatory authorities) constituting the WHO Programme for International Drug Monitoring (PIDM) contribute data to VigiBase, and UMC is the custodian in its capacity as a WHO collaborating centre for international drug monitoring.

Code availability Not applicable.

Author contributions AC: Designed and conceptualised the manuscript; analysed the EUROmediCAT data; interpreted the data; drafted the manuscript; revised the manuscript. LS, IÖ, KS, TB: generated and analysed VigiBase data; interpreted the data: drafted the manuscript; revised the manuscript. HD, ML: Coordinated the dataflow and managed EUROmediCAT registry data; made substantial contributions to the acquisition of data; interpreted the data; revised the manuscript. MA, IB, CC, EG, MG, BK, KK, AL, NL, RL, AM, OM, VN, AN, MO, AP, HR, AR, DT, AW, LY: Managed EUROmediCAT registry data; made substantial contributions to the acquisition of data; revised the manuscript. JKM: Designed and conceptualised the manuscript; supervised the study; interpreted the data; drafted the manuscript; revised the manuscript. All authors read and approved the final version.

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