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Macrolide and lincosamide antibiotic exposure in the first trimester of pregnancy and risk of congenital anomaly: A European case-control study

Aminkeng Zawuo Leke [a,*], Helen Dolk [a], Maria Loane [a], Karen Casson [a], Vera Nelen [b], Ingeborg Barišić [c], Ester Garne [d], Anke Rissman [e], Mary O'Mahony [f], Amanda J. Neville [g], Anna Pierini [h], Jorieke E.H. Bergman [i], Kari Klungsøyr [j], Anna Materna-Kiryluk [k], Anna Latos Bielenska [l], Clara Cavero Carbonell [m], Marie-Claude Addor [n], David Tucker [o]

[a] Centre for Maternal, Fetal and Infant Research, Institute for Nursing and Health Research, Ulster University, United Kingdom
[b] Provinciaal Instituut voor Hygiëne, Antwerp, Belgium
[c] Children's Hospital Zagreb, Centre of Excellence for Reproductive and Regenerative Medicine, Medical School University of Zagreb, Croatia, Zagreb, Croatia
[d] Paediatric Department Hospital, Lillebaelt Skovvangen, Kolding, Denmark
[e] Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University Magdeburg, Germany
[f] Medicine Department of Public Health, St Finbarr's Hospital Douglas Road, Cork, Ireland
[g] IMER Registry (Emila Romagna Registry of Birth Defects), Center for Clinical and Epidemiological Research, University of Ferrara - Azienda Ospedaliero - Universitaria di Ferrara, Corso della Giovecca, Ferrara, Italy
[h] Tuscany Registry of Congenital Defects, CNR Institute of Clinical Physiology/Fondazione Toscana Gabriele Monasterio, Pisa, Italy
[i] Department of Medical Genetics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[j] Medical Birth Registry of Norway, Kalfarveien, Bergen, Norway
[k] Polish Registry of Congenital Malformations, Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland
[l] Poznan University of Medical Sciences, Department of Medical Genetics, 8 Rokietnicka Street, 60-806, Poznan, Poland
[m] Rare Diseases Research Unit, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, Valencia, Spain
[n] Registre Vaudois des Malformations EUROCAT Department of Woman-Mother-Child, Maternité, Lausanne, Switzerland
[o] Congenital Anomaly Register & Information Service, Level 3 West Wing, Singleton Hospital, Sketty Lane, Swansea, United Kingdom

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ABSTRACT

This study investigated the risk of congenital heart defects (CHD) and other congenital anomalies (CA) associated with first trimester use of macrolide antibiotics (mainly erythromycin, spiramycin, clarithromycin and azithromycin) and lincosamides (clindamycin) using a case-malformed control design.

Data included 145,936 babies with a CA diagnosis (livebirths, stillbirths and terminations of pregnancy for CA) from 15 population-based EUROCAT registries in 13 European countries, covering 9 million births 1995–2012. Cases were babies with CHD, anencephaly, orofacial clefts, genital and limb reduction anomalies associated with antibiotic exposure in the literature. Controls were babies with other CA or genetic conditions. Main outcomes were odds ratios adjusted (AOR) for maternal age and registry, with 95 % Confidence Intervals (95 %CI).

Macrolide and lincosamide exposure was recorded for 307 and 28 cases, 72 and 4 non-genetic controls, 57 and 7 genetic controls, respectively. AOR for CHD was not significantly raised (AOR 0.94, 95 %CI: 0.70–1.26 vs non-genetic controls; AOR 1.01, 95 %CI: 0.73–1.41 vs genetic controls), nor significantly raised for any specific macrolide. The risk of atrioventricular septal defect was significantly raised with exposure to any macrolide (AOR 2.98; 95 %CI: 1.48–6.01), erythromycin (AOR 3.68, 95 %CI: 1.28–10.61), and azithromycin (AOR 4.50, 95 %CI: 1.30–15.58). Erythromycin, clarithromycin, azithromycin, and clindamycin were associated with an increased risk of at least one other CA.

Further research is needed on the risk of specific CA associated with macrolide and lincosamide use in the first trimester, particularly relevant for the potential use of azithromycin in the treatment of COVID-19.

* Corresponding author at: Centre for Maternal, Fetal and Infant Research, Institute for Nursing and Health Research, Ulster University, Shore Road. Newtownabbey, Co., Antrim, BT37 0QB, Northern Ireland, United Kingdom.
E-mail address: az.leke@ulster.ac.uk (A.Z. Leke).

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1. Introduction

Macrolide antibiotics are commonly used to treat respiratory problems and certain sexually transmitted diseases [1–3]. They are generally considered to have a good safety profile, but there have been conflicting findings about their potential to prolong the QT interval in ECG tests of the heart [1–4]. Azithromycin, an analogue of erythromycin, is considered to have a better safety profile than erythromycin and clarithromycin [1,4]. It has a slow-acting anti-malarial property; and owing to growing resistance to sulphadoxine-pyrimethamine (SP), its combination with chloroquine has been proposed as an alternative to the current WHO recommended intermittent preventive treatment of malaria in pregnancy with SP [5–7]. Currently, the potential use of azithromycin - chloroquine combination in COVID -19 treatment is being tested [8].

There has been debate about the potential association of macrolides (especially erythromycin) with congenital heart defects (CHD). In 2003, a Swedish Birth Registry study reported that first trimester use of macrolides (mainly erythromycin) was associated with increased risk for CHD (OR 1.79; 95 %CI 1.3–2.8) [9]. Subsequent updates of this study in 2005 and 2013 found similar results [10,11]. A recent UK study reported an increased risk of CHD (adjusted relative risk 1.62; 95 %CI 1.05–2.51) [12]. Other studies have found no significant association between macrolides and CHD [13–27], including a 2019 meta-analysis [28]. Most studies did not have an adequate sample size and power to investigate specific CHD.

Lincosamide antibiotics (the most common being clindamycin) are related to the macrolides in the WHO Anatomic Therapeutic Classification (ATC) in inhibiting bacterial protein synthesis through binding to the 50-S part of the ribosomes. There has been very little study of this antibiotic in pregnancy [24].

We investigate here the risk of CHD and other CAs associated with macrolide and lincosamide antibiotics, as part of a wider study of antibiotics using the large European EUROmediCAT database (http://www.euromedicat.eu/currentresearchanddata/data), derived from registries belonging to the EUROCAT network for Surveillance of Congenital Anomalies (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-network_en).

2. Materials and methods

2.1. Study design

The EUROmediCAT database holds data for babies with CA among live births (LB), fetal deaths (FD) from 20 weeks gestational age and terminations of pregnancy following prenatal diagnosis of fetal anomaly (TOPFA) at any gestational age. It does not include any data on babies without CA. We therefore performed a case-malformed control study. This design is particularly suitable to investigate specificity of malformation association with medication exposure rather than the overall risk of malformation [29] and has been validated in other studies using the EUROmediCAT database [29,30]. Cases were babies with CA associated in the epidemiologic literature with any antibiotic exposure (see Fig. 1). Controls were babies with other CA or genetic conditions [29]. To avoid confusion, throughout this paper the term 'registration' refers to babies/fetuses with CA including both cases and controls.

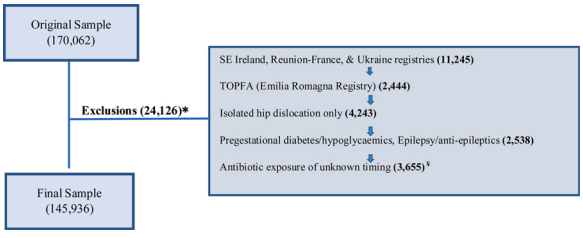

Fig. 1. Sample size flow chart.
*One baby with isolated sequence of unspecified nature was also excluded.
¥ (90 % of registrations with unknown timing were from three registries (Saxony_Anhalt_Germany, Poland, and Wielkopolska_Poland).

2.2. Study population and data

EUROmediCAT is a network dedicated to the study of medication safety in pregnancy which includes EUROCAT population-based CA registries collecting data on medication exposure during pregnancy. Currently 20 EUROCAT registries from 14 countries participate in EUROmediCAT with annual surveillance covering approximately 753,000 births per year throughout Europe (www.euromedicat.eu) [31].

The registries collect and send anonymised individual case data to the EUROmediCAT Central database. The standard data on each registration are described in EUROCAT Guide 1.4 [32]. One syndrome and up to eight malformations are coded using International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) codes with British Pediatric Association (BPA)/RCPCH one-digit extensions. Registrations have one or more major malformations, using the EUROCAT list of minor anomalies for exclusion of registrations with minor anomalies only [32]. This list of minor anomalies includes also anomalies of non-congenital origin including pyloric stenosis, and Patent Ductus Arteriosus in preterm births. All registrations are classified to EUROCAT subgroups according to their ICD9/10-RCPCH codes, as set out in EUROCAT Guide 1.4. [32] The sources used to obtain data on CA vary across registries and include maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; paediatric cardiology services; and hospital discharge and child health records [33]. The majority of the registries record anomalies diagnosed up to at least one year of age.

Medications taken in the first trimester of pregnancy are coded according to the Anatomic Therapeutic Chemical (ATC) classification. Maternal disease before and during pregnancy are recorded using ICD codes. Most registries (84 %) collect prospective data on medication exposure during the first trimester, mainly from maternity and other medical files, and some collect retrospective data from interviews with women after delivery or other sources, either alone (17 %) or in combination with prospective sources (28 %) [34]. All participating registries reviewed antibiotic exposures to confirm that they were first trimester exposures.

All registries recording information on antibiotic exposures, with data over the period of this study (1995–2012), were eligible to participate in the study. Eighteen of the 23 eligible registries agreed to participate in the study.

2.3. Dataset exclusions

We applied the following exclusions to our original dataset:

1) SE Ireland, Reunion-France and Ukraine registries were excluded because they recorded no first trimester macrolide exposure;
2) TOPFAs were excluded from the Emilia Romagna registry as information on medications is only available for LB and FD;
3) Registrations with isolated hip dislocation/dysplasia were excluded based on the known association with birthweight and potential for confounding;
4) Registrations with mothers with epilepsy or pregestational diabetes, or mothers who took anti-epileptics or hypoglycaemic agents were excluded due to the known association with CA;
5) Registrations which had antibiotic exposures of unknown timing or missing description were excluded.

These exclusions reduced the dataset from 170,062 to 145,936 registrations as shown in Fig. 1.

2.4. Case definition

Cases were defined as all LB, FD from 20 weeks gestational age, and TOPFA with major CA (classified by EUROCAT subgroup) which were signals identified from the literature, excluding those with a genetic syndrome (see Fig. 2 and Supplementary Table S1). We conducted a literature review of case-control and cohort studies reported in Medline and Reprotox databases from creation up to March 2016, to identify signals of specific CA associated with first trimester use of antibiotics. We defined a signal as a statistically significant result of increased risk, or a risk ratio ≥3, with at least two exposed cases in the first trimester [35]. As this report focuses on macrolides, the signals identified for the macrolides in the literature review (up to 2016) are shown in Table 1.

2.5. Control definition

We used two control groups:

Non-genetic controls: LB, FD from 20 weeks gestation, and TOPFA with all other major CA subgroups, excluding CA subgroups that were defined as cases or related to case CA subgroups, and excluding genetic syndromes (Fig. 2).

Genetic controls: LB, FD from 20 weeks' gestation, and TOPFA, with a diagnosis of a genetic syndrome (Fig. 2). According to EUROCAT Guide 1.4, babies with genetic syndromes are defined as those diagnosed with a genetic syndrome / microdeletion, skeletal dysplasia, or chromosomal anomaly) [32]. The genetic controls also included registrations which had a genetic syndrome where a signal anomaly was part of the genetic syndrome.

2.6. Exposures under investigation and exposure comparison groups

Exposure in first trimester of pregnancy to any macrolide (ATC code J01FA), and five specific macrolide subclasses erythromycin (ATC code J01FA01), spiramycin (ATC code J01FA02), clarithromycin (ATC code J01FA09), azithromycin (ATC code J01FA10). Clindamycin (J01FF01) was also investigated, the only lincosamide (J01FF) antibiotic represented in the dataset. Two types of exposure comparison groups were used: no antibiotic exposure during pregnancy (primary comparison) and exposure to drugs other than antibiotics, excluding vitamins and minerals (secondary comparison).

Macrolides are used as an alternative for pregnant women who are allergic to penicillins which is considered relatively safer compared to other types of antibiotics.[12] Hence we performed sensitivity analyses for selected significant results using penicillins as the exposure comparison in order to account for any residual confounding due to infection. This approach has also been used in other studies [12,18,24].

2.7. Statistical methods

Data were analysed using STATA version 12. Odds ratios (OR), crude (COR), adjusted (AOR) and 95 %CI were produced by logistic regression, with statistical significance level set at 0·05. We performed analysis for macrolides as a class, then for each of the five subclasses of macrolides. Registries without any exposures for a specific macrolide subclass were excluded from the analysis of that subclass. Each investigation of an association between a macrolide and a case CA subgroup made use of the four comparison groups i.e. the two control groups (non-genetic controls

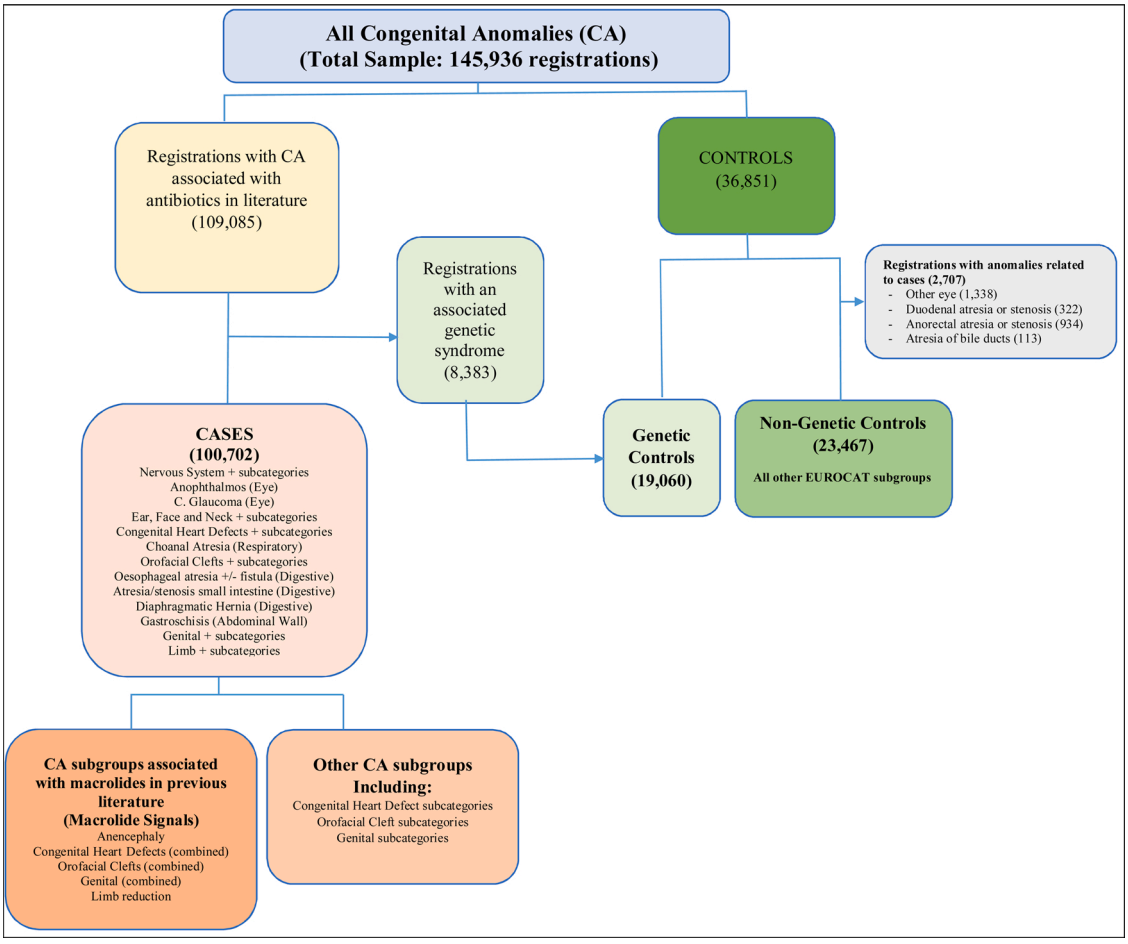

Fig. 2. Classification of EUROCAT CA subgroups according to their status as signals in previous studies (up to 2016) of antibiotics and macrolides, used in designation of case and control groups. All malformations shown are EUROCAT subgroups defined in EUROCAT Guide 1.4. [30].

Table 1
Signals for Macrolides evaluated in the study (identified in the literature up to 2016).

Macrolide studied	Signals Identified	Author/ year	Study type	Exposed events	AOR/RR (CI)
Macrolides	Congenital heart defect	Källén et al. 2003 [9]	Case-control	29	**1.79 (1.3–2.8)**
	Congenital anomalies of the genital organs	Lin et al. 2013. [20]	Case-control	6	**2.8 (1.0–7.7)**
	Any malformation	Källén et al. 2005 [10]	Cohort	103	**1.24 (1.0–1.5)**
Erythromycin	Congenital heart defect	Källén et al. 2013 [11]	Cohort	43	**1.70 (1.3–2.3)**
	Anencephaly	Crider et al. 2009 [16]	Case-control	7	**2.4 (1.1–5.3)**
	Limb deficiency	Crider et al. 2009 [16]	Case-control	14	**1.8 (1.0–3.3)**
Azithromycin	Congenital heart defect	Bar-Oz et al. 2012 [19]	Cohort	234	3.59 (0.99–12.9)
	Orofacial clefts	Cooper et al. 2008 [15]	Cohort	2	4.9 (0.90–26.6)

AOR: adjusted odds ratio; RR: relative risk; CI: confidence interval; Madeline was searched using the following MeSH and text terms combination: ('Pregnancy' OR all 'text terms') AND ('Anti-Bacterial Agents' OR all 'antibiotic class/ type') AND ('Congenital abnormality' OR all 'text terms').

and genetic controls) and the two exposure comparison groups i.e. no antibiotics exposure (primary exposure comparison) and exposed to other medications (secondary exposure comparison). We adjusted for the following confounders: year of birth in three time periods (1995–2000; 2001–2006; 2007–2012), EUROCAT registry, and maternal age in categories (<20; 20−24; 25−29; 30−34; 35−39 and 40+).

We divided our analyses into signal testing analyses regarding the five subgroups of CA shown in Table 1, and exploratory analyses regarding the non-macrolide antibiotic signal CA subgroups. For the latter, all results are given in supplementary files, and only statistically significant results with at least 3 exposed cases are given in the main tables.

We considered a result to be robust if AOR were statistically significant in two or more analyses (using the two control groups and two exposure comparison groups). Only results involving the primary exposure comparison group are presented (results involving secondary exposure comparison are found in the Supplementary Tables S4b–9b).

As our primary controls (non-genetic controls) are malformed babies, there is a possibility that some CA in this control group could be associated with the macrolides under investigation (teratogen non-specificity bias), leading to reduced OR [36,37]. As a sensitivity analysis, we therefore investigated the association between specific non-genetic control subgroups and macrolides using the secondary controls (genetic controls) as the comparison group. These results are given in the Supplementary Table S3.

3. Results

3.1. Study population

Our analysis dataset consisted of 145,936 registrations from 15 EUROCAT registries in 13 European countries covering an 18-year period (1995–2012) and included 100,702 cases, 23,467 non-genetic controls and 19,060 genetic controls (Table 2). A total of 2707 registrations with CA subgroups related to that of cases were excluded from the analysis (Fig. 2).

During the first trimester, a total of 3440 (2.36 %) women were exposed to at least one antibiotic (Supplementary Table S2). First trimester infection was reported for 2499 (1.71 %) women of whom 14.77 % had a record of first trimester antibiotic exposure.

Cases significantly differed from both control groups with respect to registry and maternal age (Table 2). Cases and controls also differed by type of birth, since the proportion of TOPFA varies by type of anomaly.

3.2. Signal testing and exploratory analysis

Overall, the proportion of cases (0.30 %) exposed to macrolides in the first trimester was not significantly different to that of non-genetic controls (0.29 %; AOR 0.99; 95 %CI 0.76–1.28), or genetic controls (0.28 %; AOR 1.04; 95 %CI 0.77–1.40). Similar results were also obtained for all five specific macrolides studied (Table 3).

None of the 5 signals shown in Table 1 were confirmed (Table 3). However, although the CHD signal was not confirmed, a pattern of increased risk for the specific heart defect atrioventricular septal defect (AVSD) was observed for any macrolide exposure (9 exposed cases, AOR 2.98; 95 %CI 1.48–6.01); erythromycin (4 exposed cases, AOR 3.68; 95 %CI 1.28–10.61); clarithromycin (2 exposed cases, AOR 6.85; 95 %CI 1.41–33.32; see foot notes in Table 4); and azithromycin (3 exposed cases, AOR 4.50; 95 %CI 1.30–15.58) (Table 4). These associations were robust across both control and exposure comparison groups (see also Supplementary Tables S4, S5, S7 and S8).

Since the 2016 literature review generating the signal CA, one further study has generated new signals: urinary system with all macrolides and respiratory system with moxifloxacin [25]. These CA subgroups were both included among non-genetic controls. When evaluated for macrolide exposure, there was no evidence of any increased risk for these CA subgroups compared to genetic controls: urinary system (AOR 0.87 95 %CI 0.55–1.39); respiratory system (AOR 0.44; 95 %CI 0.10–1.89) (Supplementary Table S3).

In the exploratory analyses of signal CA subgroups previously associated with other antibiotics, four associations were found (Table 3): erythromycin with diaphragmatic hernia (5 exposed cases, AOR 3.19; 95 %CI 1.22–8.32); clarithromycin with orofacial clefts (8 exposed cases, AOR 2.94; 95 %CI 1.04–8.30); azithromycin with syndactyly (8 exposed cases, AOR 3.80; 95 %CI 1.62–8.94); and clindamycin with hydrocephalus (3 exposed cases, AOR 6.63; 95 %CI 1.46, 30.18).

3.3. Sensitivity analysis

Sensitivity analyses for all significantly elevated risks using penicillins as the exposure comparison group, gave AOR similar or greater than that obtained for no antibiotics (primary exposure comparison), although with less precision (Table 4). The study results were also not altered when we excluded the three registries with a high proportion of excluded registrations due to unknown antibiotic timing from the analyses.

The overall risk for non-genetic controls as a group was not raised compared to genetic controls (AOR 1.01; 95 %CI 0.69–1.46), confirming absence of strong macrolide associations in this control group. With regard to specific CA in the non-genetic control group, we found an increased risk with macrolide exposure for teratogenic syndromes with malformations (AOR 6.50; 95 %CI 1.92–22.03) explained by its

Table 2
Comparison of selected maternal characteristics between cases and control groups.

Maternal/fetal characteristics	Cases n (%)	Non-genetic controls n (%)	Chi-Squared P-value	Genetic controls n (%)	Chi-Squared P-value
Total	100702 **(70.31)**	23467 **(16.38)**		19060 **(13.31)**	
Maternal age group (years)			**≤0.001**		**≤0.001**
>20	4813 (4.78)	941 (4.01)		474 (2.49)	
20-24	19214 (19.08)	3,844 (16.38)		1846 (9.69)	
25-29	29947 (29.74)	7,073 (30.14)		3651 (19.16)	
30-34	26830 (26.64)	6,822 (29.07)		4562 (23.93)	
35-39	13049 (12.96)	3,312 (14.11)		4990 (26.18)	
40+	3059 (3.04)	763 (3.25)		3011 (15.80)	
Unknown	3790 (3.76)	712 (3.03)		526 (2.76)	
Type of birth			**≤0.001**		**≤0.001**
Live birth	95595 (94.93)	22014 (93.81)		12,992 (68.16)	
Stillbirth/fetal deaths	1072 (1.06)	306 (1.30)		466 (2.44)	
TOPFA	4033 (4.00)	1147 (4.89)		5,599 (29.38)	
Not known	2 (0.00)	0 (0.00)		3 (0.02)	
Registry			**≤0.001**		**≤0.001**
Odense_Denmark	1,643 (1.63)	338 (1.44)		494 (2.59)	
Tuscany_Italy	7,069 (7.02)	1,843 (7.85)		1,679 (8.81)	
N Netherlands_Netherlands	4,719 (4.69)	1,267 (5.40)		1,547 (8.12)	
Emilia_Romagna_Italy	6,153 (6.11)	1,820 (7.76)		928 (4.87)	
Vaud_Switzerland	2,501 (2.48)	1,118 (4.76)		931 (4.88)	
Zagreb_Croatia	1,434 (1.42)	309 (1.32)		218 (1.14)	
Antwerp_Belgium	4,303 (4.27)	1,928 (8.22)		1,078 (5.66)	
Saxony_Anhalt_Germany	2,962 (2.94)	639 (2.72)		418 (2.19)	
Cork_&_Kerry_Ireland	2,196 (2.18)	381 (1.62)		710 (3.73)	
Wales_United_Kingdom	11,148 (11.07)	3,523 (15.01)		2,701 (14.17)	
Norway_Norway	7,301 (7.25)	1,316 (5.61)		1,122 (5.89)	
Wielkopolska_Poland	9,503 (9.44)	1,837 (7.83)		1,112 (5.83)	
Poland_Poland	35,118 (34.87)	5,652 (24.08)		4,729 (24.81)	
French_West_Indies-France	428 (0.43)	167 (0.71)		256 (1.34)	
Valencia_Spain	4,224 (4.19)	1,329 (5.66)		1,137 (5.97)	

subcategory maternal infections resulting in malformations (OR 6.44; 95 %CI 1.89–21.92) (Supplementary Table S3). These are recognised infection syndromes such as congenital rubella/CMV/toxoplasmosis, where antibiotic use may be expected, but numbers are very small. Results from further analysis after excluding these teratogenic syndromes from the controls were similar to the original study results.

The study results were similar when the analyses were restricted to case subgroups with isolated CA, and when genetic controls with signal anomalies were excluded.

4. Discussion

4.1. Main findings

In this large EUROmediCAT study, we did not find evidence of a strong association between CHD and macrolide exposure. However, we did find evidence regarding a threefold or more raised risk of AVSD specifically, significantly associated with three types of macrolide, robust across analyses with different control groups and exposure comparison groups. AVSD accounts for 2% of CHD cases in EUROCAT data, so it is not surprising this does not affect the overall CHD finding. AVSD are common in babies with Down syndrome, but none of the exposed AVSD cases had Down syndrome. The majority of negative studies regarding macrolides and CHD [13–25], as well as those that found an association [9–12], did not have enough power to investigate specific subgroups of CHD. We found only one study (Crider et al. 2009) [16] that has investigated the association between AVSD and erythromycin and found an elevated risk, although not statistically significant (AOR 2.2, CI: 0.8–6.1). This was a case-control study which obtained exposure information retrospectively by interview, a considerable time after exposure, thus possibly underestimating ORs.

There is evidence from animal and human studies that suggests macrolides could have a link with some CHDs [10]. At clinical concentrations, macrolides can inhibit a specific cardiac potassium current (IKr) channel, expressed by hERG (human ether a-go-go related gene). This can then lead to a prolonged QT interval, causing a type of ventricular tachycardia called *torsades de pointes* (TdP) [4,38]. In a developing rat embryo, particularly during the period before the heart is inverted (corresponding to weeks 5–9 of human pregnancy), TdP can result in pressure changes and misdirection of blood flow in the developing cardiovascular system, that can in turn lead to hypoxia and re-oxygenation damage resulting in septal and other vessel defects [39–43].

In further exploratory analysis of our data we found elevated risk of diaphragmatic hernia, orofacial clefts, syndactyly, associated with first trimester use of erythromycin, clarithromycin, and azithromycin, respectively. None of these associations have been previously reported. However, multiple testing may have produced some spuriously significant results, and independent confirmation is necessary.

We could not confirm previously reported associations of macrolides with genital anomalies, [20] erythromycin with anencephaly [16] and limb deficiency [16], and azithromycin with orofacial clefts [15]. Since our 2016 literature search, a new study found an association of urinary system defects with erythromycin (AOR 2.12, CI: 1.08–4.17) [24], which our data and other studies did not support [11,20,44–46].

Our investigation of spiramycin did not find an association with any of the CAs studied, but this was the least frequent exposure and we had limited statistical power. We found only one study from the literature that investigated spiramycin, finding no increased risk [26]. Further studies are needed on the teratogenic potential of this macrolide antibiotic.

The only lincosamide antibiotic reported in our study population was clindamycin. A study in Quebec found an association between clindamycin exposure and musculoskeletal anomalies (a combination of limb defects, craniosynostosis, skeletal dysplasias and abdominal wall defects which is a large heterogeneous group), as well as an association with a combination of ventricular septal defects, atrial septal defects and atrioventricular septal defects [24]. We did not find evidence of these associations among the CA subgroups we studied. We did however find an association with hydrocephalus, again an exploratory finding which needs confirmation in an independent dataset. There is very little published safety data regarding clindamycin [24].

Table 3
Crude and AOR for the association between macrolides/clindamycin and each CA subgroup, using the primary exposure comparison (non-exposed), for macrolide signal CA and for CA previously associated with other antibiotics*.

	Total	Exposed n (%)	Non-Genetic Controls				Genetic Controls			
			Crude model		Adjusted model[a]		Crude model		Adjusted model[a]	
			OR	95 %CI	OR	95 %CI	OR	95 %CI	OR	95 %CI
Macrolides_J01FA										
Non-Genetic Controls	23,467	72 (0.29)								
Genetic Controls	19,060	57 (0.28)								
All cases	100,702	304 (0.30)	0.98	[0.76, 1.27]	0.99	[0.76, 1.28]	1.01	[0.76, 1.34]	1.04	[0.77, 1.40]
Literature signal for macrolides										
Congenital heart defects	46,169	129 (0.28)	0.91	[0.68, 1.22]	0.94	[0.70, 1.26]	0.93	[0.68, 1.28]	1.01	[0.73, 1.41]
Genital	12,450	40 (0.32)	1.05	[0.71, 1.54]	0.96	[0.65, 1.42]	1.07	[0.72, 1.61]	0.95	[0.61, 1.46]
Exploratory analyses of other antibiotic signal CA										
Atrioventricular septal defect	1,027	9 (0.88)	**2.87**	**[1.43, 5.76]**	**2.98**	**[1.48, 6.01]**	**2.95**	**[1.46, 5.97]**	**3.09**	**[1.48, 6.44]**
Erythromycin_J01FA01										
Non-Genetic Controls	20345	28 (0.11)								
Genetic Controls	16761	18 (0.09)								
All cases	88270	119 (0.13)	0.98	[0.65, 1.48]	1.00	[0.66, 1.52]	1.26	[0.76, 2.06]	1.30	[0.78, 2.17]
Literature signal for erythromycin										
Congenital heart defects	39247	54 (0.14)	1.00	[0.63, 1.58]	1.05	[0.66, 1.67]	1.28	[0.75, 2.19]	1.38	[0.79, 2.40]
Anencephalus and similar	1213	2 (0.16)	1.20	[0.29,5.04]	1.02	[0.24,4.32]	1.54	[0.36,6.63]	1.12	[0.25,5.05]
Limb reduction	3121	4 (0.13)	0.93	[0.33, 2.66]	1.27	[0.44, 3.66]	1.19	[0.40, 3.53]	1.31	[0.42, 4.08]
Exploratory analyses of other antibiotic signal CA										
Atrioventricular septal defect	932	4 (0.43)	**3.13**	**[1.09, 8.94]**	**3.68**	**[1.28, 10.61]**	**4.01**	**[1.35, 11.87]**	**4.30**	**[1.40, 13.19]**
Diaphragmatic hernia	1215	5 (0.41)	**3.00**	**[1.16, 7.78]**	**3.19**	**[1.22, 8.32]**	**3.84**	**[1.42, 10.37]**	**3.47**	**[1.25, 9.66]**
Clarithromycin_J01FA09¥										
Non-Genetic Controls	11898	7 (0.03)								
Genetic Controls	10005	2 (0.01)								
All cases	60360	32 (0.05)	0.90	[0.40, 2.04]	1.17	[0.51, 2.65]	2.65	[0.64, 11.06]	2.68	[0.63, 11.34]
Exploratory analyses of other antibiotic signal CA										
Oro-facial clefts	6278	8 (0.13)	2.17	[0.79, 5.98]	**2.94**	**[1.04, 8.30]**	**6.38**	**[1.35, 30.06]**	**7.22**	**[1.47, 35.37]**
Cleft lip with or without palate	3822	5 (0.13)	2.23	[0.71, 7.02]	3.12	[0.96, 10.16]	**6.55**	**[1.27, 33.78]**	**7.43**	**[1.35, 40.82]**
Cleft palate	2456	3 (0.12)	2.08	[0.54, 8.04]	2.45	[0.62, 9.75]	**6.12**	**[1.02, 36.63]**	**6.81**	**[1.11, 41.74]**
Azithromycin_J01FA10										
Non-Genetic Controls	13325	17 (0.07)								
Genetic Controls	11154	20 (0.10)								
All cases	64295	79 (0.12)	0.96	[0.57,1.63]	1.14	[0.67, 1.94]	0.68	[0.42, 1.12]	0.85	[0.50, 1.43]
Literature signal for azithromycin										
Congenital heart defects	28,735	27 (0.09)	0.74	[0.40,1.35]	0.90	[0.49,1.65]	0.52	[0.29,0.93]	0.66	[0.35,1.23]
Oro-facial clefts	6,596	6 (0.09)	0.71	[0.28, 1.81]	0.89	[0.35, 2.28]	0.51	[0.20, 1.26]	0.54	[0.21, 1.40]
Exploratory analyses of other antibiotic signal CA										
Atrioventricular septal defect	657	3 (0.46)	**3.59**	**[1.05, 12.28]**	**4.50**	**[1.30, 15.58]**	2.55	[0.76, 8.62]	2.74	[0.78, 9.63]
Syndactyly	2,211	8 (0.36)	**2.84**	**[1.23, 6.59]**	**3.80**	**[1.62, 8.94]**	2.02	[0.89, 4.60]	2.18	[0.92, 5.21]
Clindamycin_J01FF01										
Non-Genetic Controls	13325	4 (0.02)								
Genetic Controls	11154	7 (0.03)								
All cases	67018	28 (0.04)	1.38	[0.48, 3.94]	1.40	[0.49, 4.01]	0.63	[0.28, 1.44]	0.72	[0.30, 1.72]
Exploratory analyses of other antibiotic signal CA										
Hydrocephalus	1,656	3 (0.18)	**6.00**	**[1.34, 26.82]**	**6.63**	**[1.46, 30.18]**	2.74	[0.71, 10.61]	4.1	[0.97, 17.32]

* Signal CA associated with other antibiotics – only statistically significant results with at least three exposed cases shown, Other results in Supplementary Tables S3-9; a Adjusted for year of birth, EUROCAT Registry and maternal age ; ¥ Showed elevated risk of atrioventricular septal defect based on 2 exposed cases **(AOR 6.85, CI: 1.41 – 33.32)**; Original signals are in italics.; Anophthalmia had increased Odds ratios, but this was based on one or two exposed cases (See Supplementary Table S4-9); Numbers in the comparison groups vary because for each specific antibiotic, registries without any exposures were excluded; Data for Spiramycin - J01FA02 presented in Supplementary Table S6.

Safety advice about the use of macrolides during pregnancy varies across different countries. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency advises alternatives to clarithromycin and azithromycin should be prescribed during pregnancy [47]. Our results support this position.

4.2. Strengths and limitations

The major strengths of our study include the population based data, large sample size, detailed and standardised data on CA, and inclusion of TOPFA, which constitute a large proportion of some CAs [48]. Additionally, exposures were mainly prospectively ascertained, and our case-malformed control design limits recall and information bias, especially for the small proportion of retrospectively ascertained exposures [29]. Our study was hypothesis driven, and the use of two control and exposure comparison groups together with sensitivity analysis, allowed us to evaluate the robustness of any associations.

Our study also had some limitations. Exposure to antibiotics (2.36 %) was low, compared with the expected 3–14 % rate of first trimester antibiotic exposure in the European population [9,18,49]. This suggests antibiotic exposures were under-ascertained in our data, as was shown also in a study comparing the registry data to linked prescription data [50]. However, the reporting of antibiotic exposures would not have been different between cases and controls, and is not a plausible explanation for a specific increased risk of AVSD.

We had very little data about the indication for prescribing, or about untreated infection, so we could not examine confounding by indication in this way. Our sensitivity analysis comparing macrolide use with penicillins obtained similar results to that with the primary exposure comparison. Since macrolides and penicillins are commonly used for the same indication, this suggests that the excess risk we found relates to macrolides rather than the underlying infection. Other studies have used

Table 4
Selected risk estimates for first trimester macrolide exposure compared with no antibiotic or first trimester penicillin exposure.

	Macrolides vs No antibiotic (Primary)		Macrolides vs penicillins	
	AOR	CI	AOR	CI
Macrolides_J01FA				
Atrioventricular septal defect	**2.98**	**[1.48, 6.01]**	**4.51**	**[1.71, 11.94]**
Erythromycin_J01FA01				
Atrioventricular septal defect	**3.68**	**[1.28, 10.61]**	**4.24**	**[1.22, 14.68]**
Diaphragmatic hernia	**3.19**	**[1.22, 8.32]**	**4.72**	**[1.51, 14.71]**
Clarithromycin_J01FA09				
Oro-facial clefts	**2.94**	**[1.04, 8.30]**	2.23	[0.78, 6.37]
Azithromycin_J01FA10				
Atrioventricular septal defect	**4.50**	**[1.30, 15.58]**	**4.41**	**[1.04, 18.71]**
Syndactyly	**3.80**	**[1.62, 8.94]**	**3.74**	**[1.45, 9.65]**
Clindamycin_J01FF01				
Hydrocephalus	**6.63**	**[1.46, 30.18]**	**6.42**	**[1.33, 31.04]**

this same approach as a proxy to account for residual confounding by indication [11,18,24].

The case-malformed control design is open to teratogen non-specificity bias, if the controls include CA which are associated with the exposure [29]. We examined evidence of teratogen non-specificity bias and found no evidence of such bias; results were similar for the secondary comparison between cases and genetic controls which cannot be associated with first trimester medication exposure; there were no specific CA among the controls showing an association with macrolide exposure when compared to genetic controls; and results were similar after excluding the few cases of congenital infection syndromes.

Finally, we conducted many tests with some significant findings therefore possible by chance. We chose the strategy of specifying our hypotheses in advance [51] corresponding to previous signals, and rather than increasing the risk of Type 2 errors in exploratory analyses aimed at signal detection, we recommend confirmation of these new findings in independent datasets.

5. Conclusion

Our investigation did not find evidence to support the five CA signals related to macrolides found in the literature. While a positive association was not found between CHD as a group and macrolides, an elevated risk was found between macrolides and specific macrolides (erythromycin, clarithromycin and azithromycin) and AVSD. We also found elevated risk for other anomalies associated with first trimester use of specific macrolides and clindamycin that need further follow up in independent datasets.

Contribution to authorship

AZL, HD, ML and KC conceptualised the study. VN, IB, EG, HR, AR, MO, AJN, AP,JEHB, KK, AMK, ALB,CCC, MCA, DT extracted data and verified all first trimester exposures. LAZ conducted the literature review and data analysis with technical inputs from HD, ML and KC. AZL, HD drafted the manuscript with full inputs from all other authors.

Ethical approval

This study was approved by the INHR Ethics Committee in Ulster University on the 11th of March 2012. All contributing registries have their own ethics approval arrangements appropriate to their national and local ethics guidelines.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2021.01.006.

References

[1] J. Giudicessi, M. Ackerman, Azithromycin and risk of sudden cardiac death: Guilty as charged or falsely accused? Cleve. Clin. J. Med. 80 (9) (2013) 539–544.
[2] E. Gorelik, R. Masarwa, A. Perlman, V. Rotshild, M. Muszkat, I. Matok, Systematic review, meta-analysis, and network meta-analysis of the cardiovascular safety of macrolides, Antimicrob. Agents Chemother. 62 (6) (2018).
[3] L. Polgreen, B. Riedle, J. Cavanaugh, S. Girotra, B. London, M. Schroeder, et al., Estimated cardiac risk associated with macrolides and fluoroquinolones decreases substantially when adjusting for patient characteristics and comorbidities, J. Am. Heart Assoc. 7 (9) (2018).
[4] D. Juurlink, The cardiovascular safety of azithromycin, Can. Med. Assoc. J. 186 (15) (2014) 1127–1128.
[5] R. Chico, R. Pittrof, B. Greenwood, D. Chandramohan, Azithromycin-chloroquine and the intermittent preventive treatment of malaria in pregnancy, Malar. J. 7 (1) (2008).
[6] WHO Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-pyrimethamine (IPTp-SP) [Internet], World Health Organization, 2014 [cited 1 June 2020]. Available from: https://www.who.int/malaria/publications/atoz/policy_brief_iptp_sp_policy_recommendation/en/.
[7] J. Kimani, K. Phiri, S. Kamiza, S. Duparc, A. Ayoub, R. Rojo, et al., Efficacy and safety of azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of plasmodium falciparum malaria infection in pregnant women in Africa: an open-label, randomized trial, PLoS One 11 (6) (2016), e0157045.
[8] T.F. Simpson, J.R. Kovacs, C.E. Stecker, Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19 - American College of Cardiology [Internet] [cited 1 June 2020]. Available from:, American College of Cardiology, 2020 https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19.
[9] B. Kallen, Maternal drug use in early pregnancy and infant cardiovascular defect, Reprod. Toxicol. 17 (3) (2003) 255–261.
[10] B. Källén, O.P. Otterblad, B. Danielsson, Is erythromycin therapy teratogenic in humans? Reprod. Toxicol. 20 (2) (2005) 209–214.
[11] B. Källén, B. Danielsson, Fetal safety of erythromycin. An update of Swedish data, Eur. J. Clin. Pharmacol. 70 (3) (2013) 355–360.
[12] H. Fan, R. Gilbert, F. O'Callaghan, L. Li, Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study, BMJ (2020) 331.
[13] R. Tellem, S. Shechtman, J. Arnon, Pregnancy outcome after gestational exposure to the new macrolides: a prospective controlled cohort study, Reprod. Toxicol. 20 (2005) 484–485.
[14] B. Bar-Oz, O. Diav-Citrin, S. Shechtman, R. Tellem, J. Arnon, I. Francetic, et al., Pregnancy outcome after gestational exposure to the new macrolides: a prospective multi-center observational study, Eur. J. Obstet. Gynecol. Reprod. Biol. 141 (1) (2008) 31–34.
[15] W.O. Cooper, S. Hernandez-Diaz, P.G. Arbogast, J.A. Dudley, S.M. Dyer, P. S. Gideon, K.S. Hall, L.A. Kaltenbach, W.A. Ray, Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations, Paediatr. Perinat. Epidemiol. 23 (1) (2009) 18–28.
[16] K.S. Crider, M.A. Cleves, J. Reefhuis, R.J. Berry, C.A. Hobbs, D.J. Hu, Antibacterial medication use during pregnancy and risk of birth defects: national Birth Defects Prevention Study, Arch. Pediatr. Adolesc. Med. 163 (11) (2009) 978–985.
[17] H. Nordeng, M. Romøren, M. Lindbæk, Safety of macrolides during pregnancy—With special focus on erythromycin and congenital heart malformations, Reprod. Toxicol. 2 (30) (2010) 227.
[18] M. Romøren, M. Lindbæk, H. Nordeng, Pregnancy outcome after gestational exposure to erythromycin–a population-based register study from Norway, Br. J. Clin. Pharmacol. 74 (6) (2012) 1053–1062.

[19] B. Bar-Oz, C. Weber-Schoendorfer, M. Berlin, M. Clementi, E. Di Gianantonio, L. de Vries, M. De Santis, P. Merlob, B. Stahl, G. Eleftheriou, E. Mañáková, The outcomes of pregnancy in women exposed to the new macrolides in the first trimester, Drug Saf. 35 (7) (2012) 589–598.
[20] K.J. Lin, A.A. Mitchell, W.P. Yau, C. Louik, S. Hernández-Díaz, Safety of macrolides during pregnancy, Am. J. Obstet. Gynecol. 208 (3) (2013), 221-e1.
[21] J.T. Andersen, M. Petersen, E. Jimenez-Solem, J.N. Rasmussen, N.L. Andersen, S. Afzal, K. Broedbaek, B.R. Hjelvang, L. Køber, C. Torp-Pedersen, H.E. Poulsen, Trimethoprim use prior to pregnancy and the risk of congenital malformation: a register-based nationwide cohort study, Obstet. Gynecol. Int. 2013 (2013).
[22] A.B. Dinur, G. Koren, I. Matok, A. Wiznitzer, E. Uziel, R. Gorodischer, A. Levy, Fetal safety of macrolides, Antimicrob. Agents Chemother. 57 (7) (2013) 3307–3311.
[23] A. Bérard, O. Sheehy, J.P. Zhao, H. Nordeng, Use of macrolides during pregnancy and the risk of birth defects: a population-based study, Pharmacoepidemiol. Drug Saf. 24 (12) (2015) 1241–1248.
[24] F.T. Muanda, O. Sheehy, A. Bérard, Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study, Br. J. Clin. Pharmacol. 83 (11) (2017) 2557–2571.
[25] P. Damkier, L.M. Brønniche, J.F. Korch-Frandsen, A. Broe, In utero exposure to antibiotics and risk of congenital malformations: a population-based study, Am. J. Obstet. Gynecol. 221 (6) (2019), 648-e1.
[26] A.E. Czeizel, M. Rockenbauer, J. Olsen, H.T. SØRENSEN, A case-control teratological study of spiramycin, roxithromycin, oleandomycin and josamycin, Acta Obstet. Gynecol. Scand. 79 (3) (2000) 234–237.
[27] A.E. Czeizel, M. Rockenbauer, H.T. Sørensen, J. Olsen, A population-based case-control teratologic study of oral erythromycin treatment during pregnancy, Reprod. Toxicol. 13 (6) (1999) 531–536.
[28] N. Mallah, H.R. Tohidinik, M. Etminan, A. Figueiras, B. Takkouche, Prenatal exposure to macrolides and risk of congenital malformations: a meta-analysis, Drug Saf. 12 (2019), 1-1.
[29] Helen Dolk, Anthony Wemakor, Response to: case–control studies require appropriate population controls: an example of error in the SSRI birth defect literature, Eur. J. Epidemiol. (2015) 1219–1221.
[30] Janneke Jentink, Maria A. Loane, Helen Dolk, Ingeborg Barisic, Ester Garne, Joan K. Morris, Lolkje T.W. de Jong-van den Berg, Valproic acid monotherapy in pregnancy and major congenital malformations, N. Engl. J. Med. 362 (23) (2010) 2185–2193.
[31] L.T. de Jong-van den Berg, M.K. Bakker, H. Dolk, EUROmediCAT: European surveillance of safety of medication use in pregnancy, Pharmacoepidemiol. Drug Saf. 20 (S1) (2011) S46–7.
[32] EUROCAT Guide 1.4 Reference Documents [Internet], 2018 [cited 1 June 2020]. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Full_Guide_1_4_version_28_DEC2018.pdf.
[33] R. Greenlees, A. Neville, M.C. Addor, E. Amar, L. Arriola, M. Bakker, I. Barisic, P. A. Boyd, E. Calzolari, B. Doray, E. Draper, Paper 6: EUROCAT member registries: organization and activities, Birth Defects Res. Part A Clin. Mol. Teratol. 91 (S1) (2011) S51–100.
[34] M. Bakker, L. De Jonge, EUROCAT Special Report: Sources of Information on Medication Use in Pregnancy, EUROCAT Central Registry, 2014.
[35] A.Z. Leke, Maternal Use and Safety of Anti-Infectives in Pregnancy, with Special Reference to Cameroon Doctoral Dissertation, Ulster University, 2017, p. 159. Chapter 4.
[36] K.J. Rothman, S. Greenland, T.L. Lash (Eds.), Modern Epidemiology, Lippincott Williams & Wilkins, 2008.
[37] E.B. Hook, What kind of controls to use in case control studies of malformed infants: recall bias versus "teratogen nonspecificity" bias, Teratology 61 (5) (2000) 325–326.
[38] R. Webster, D. Leishman, D. Walker, Towards a drug concentration effect relationship for QT prolongation and torsades de pointes, Curr. Opin. Drug Discov. Dev. 5 (1) (2002) 116–126.
[39] C. Danielsson, J. Brask, A.C. Sköld, R. Genead, A. Andersson, U. Andersson, K. Stockling, R. Pehrson, K.H. Grinnemo, S. Salari, H. Hellmold, Exploration of human, rat, and rabbit embryonic cardiomyocytes suggests K-channel block as a common teratogenic mechanism, Cardiovasc. Res. 97 (1) (2013) 23–32.
[40] M.P. Davies, R.H. An, P. Doevendans, S. Kubalak, K.R. Chien, R.S. Kass, Developmental changes in ionic channel activity in the embryonic murine heart, Circ. Res. 78 (1) (1996) 15–25.
[41] L. Wang, Z.P. Feng, C.S. Kondo, R.S. Sheldon, H.J. Duff, Developmental changes in the delayed rectifier K+ channels in mouse heart, Circ. Res. 79 (1) (1996) 79–85.
[42] C. Abrahamsson, M. Palmer, B. Ljung, G. Duker, C. Bäärnhielm, L. Carlsson, B. Danielsson, Induction of rhythm abnormalities in the fetal rat heart. A tentative mechanism for the embryotoxic effect of the class III antiarrhythmic agent almokalant, Cardiovasc. Res. 28 (3) (1994) 337–344.
[43] O.C. Jaffee, Hemodynamic factors in the development of the chick embryo heart, Anat. Rec. 151 (1) (1965) 69–75.
[44] C. Louik, M.M. Werler, A.A. Mitchell, Erythromycin use during pregnancy in relation to pyloric stenosis, Am. J. Obstet. Gynecol. 186 (2) (2002) 288–290.
[45] M. Lund, B. Pasternak, R.B. Davidsen, B. Feenstra, C. Krogh, L.J. Diaz, J. Wohlfahrt, M. Melbye, Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study, BMJ 348 (2014) g1908.
[46] W.O. Cooper, W.A. Ray, M.R. Griffin, Prenatal prescription of macrolide antibiotics and infantile hypertrophic pyloric stenosis, Obstet. Gynecol. 100 (1) (2002) 101–106.
[47] Joint Formulary Committee, BNF 77 (British National Formulary) March 2019, Pharmaceutical Press, 2019.
[48] E. Garne, H. Dolk, M. Loane, P.A. Eurocat, EUROCAT Website Data on Prenatal Detection Rates of Congenital Anomalies, 2010.
[49] I. Petersen, R. Gilbert, S. Evans, A. Ridolfi, I. Nazareth, Oral antibiotic prescribing during pregnancy in primary care: UK population-based study, J. Antimicrob. Chemother. 65 (10) (2010) 2238–2246.
[50] L. de Jonge, E. Garne, R. Gini, S.E. Jordan, K. Klungsoyr, M. Loane, A.J. Neville, A. Pierini, A. Puccini, D.S. Thayer, D. Tucker, Improving information on maternal medication use by linking prescription data to congenital anomaly registers: a EUROmediCAT study, Drug Saf. 38 (11) (2015) 1083–1093.
[51] Sander Greenland, Analysis goals, error-cost sensitivity, and analysis hacking: essential considerations in hypothesis testing and multiple comparisons, Paediatr Perinatal Epidemiol. (2020).