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ORIGINAL RESEARCH ARTICLE

Identifying Associations between Maternal Medication Use and Birth Defects Using a Case-Population Approach: An Exploratory Study on Signal Detection

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Abstract

Background The effects of many drugs on the unborn child are unknown. In a case-population design, drug exposure of cases is compared with that of a source population; this kind of study can be useful for generating signals.

Objective To see whether a comparison of drug use rates from the birth defect registry EUROCAT NNL (cases) with prescription rates from a population-based prescription database, the IADB (population), could be used to detect signals of teratogenic risk of drugs.

Methods We defined 3,212 cases from the EUROCAT NNL database, a population-based birth defect registry in the Northern Netherlands and 29,223 population controls from the IADB, a prescription database with data from community pharmacies in the same geographical area, born between 1998 and 2008. We classified the malformations of the 3,212 cases into several malformation groups according to organ system (based on the International Classification of Diseases codes and the EUROCAT guidelines). If a child had multiple malformations in several organ systems ($n = 253$, 7.9 %), he/she was counted in all the categories represented. For several groups of malformations we calculated rate ratios (RR) and 95 % confidence intervals for drugs acting on the central nervous system and for drugs considered to be safe for use in pregnancy. The RRs were based on first-trimester drug use rates from the cases in the EUROCAT NNL database and prescription rates from the population controls in the IADB.

Results For drugs acting on the central nervous system we found significantly increased RRs for the anti-epileptic drug valproic acid and for some selective serotonin reuptake inhibitors. For drugs considered to be safe only the antihypertensive methyldopa showed significantly increased RRs.

Conclusion We show that a case-population study is a suitable method for detecting signals of possible teratogenicity, provided that the teratogenic effects and the drugs under study are as specific as possible and the drugs are widely used.

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1 Background

The first trimester of pregnancy is the critical period for the developing embryo, because the organogenesis takes place during these first weeks [1]. Many pregnant women use at least one drug on prescription during this first trimester with estimations varying between 22 % and 54 % [1–4]. However, for many drugs on the market, the effects on the unborn child still have to be established. Because results from animal studies do not always predict teratogenicity in

humans and pregnant women are excluded from pre-marketing trials for ethical reasons, post-marketing surveillance is necessary [5–7].

When a drug enters the market, it takes some time before enough pregnant women are exposed to it and a proper cohort or case-control study can be performed. At first, mainly case reports or case series will be found in the literature. Several pharmaco-epidemiological approaches have been established for rapidly identifying any adverse drug effects, like the case-population and case-cohort designs [8–11]. The case-population or population-based case-cohort approach compares past exposure to a given risk factor in subjects presenting with a given disease or symptom (cases) with the exposure rate to this factor in the source population or in the whole cohort [11]. This design can detect rare but serious adverse drug reactions not discovered by clinical trials and has predominantly been used in post-marketing surveillance of adverse drug effects [8–11]. Conditional on having a representative source population, case-population studies are relatively rapid and inexpensive. For an estimation of exposure to the drug under study in the population the cases come from, general consumption data are used [10]. The main limitation of this approach is that general consumption data are often not available.

In this study, we explored whether a case-population design can be used to detect signals of teratogenicity as well, by comparing cases from a population-based birth defect registry with controls derived from a population-based prescription database.

2 Methods

2.1 Cases

Cases were selected from EUROCAT NNL, a population-based birth defect registry in the northern part of the Netherlands, covering approximately 10 % of all births in the country. A child can be registered in the database up to the age of 16 years, there is no lower age limit. All types of births are included in the registry: live births, stillbirths, spontaneous abortions and terminations of pregnancy [12].

Parental informed consent is required for registration. Approximately 80 % of the parents agree with inclusion of their child in the registry. Parents are asked to complete a questionnaire with questions about sociodemographic characteristics, prenatal screening methods and diagnostic tests, and exposure to possible risk factors (such as chemicals or recreational drugs).

Maternal permission is required to obtain the mother's pharmacy records for the period of 3 months before conception until delivery. Actual use of the prescribed medication is verified in a telephone interview and only the actually used medication is registered [12].

Table 1 Number of cases classified into the different malformation groups

Malformation group	Cases *n* (% of 3,212)
Malformations of the central nervous system	208 (6.4)
Cardiac malformations	873 (27.2)
Clefts	294 (9.2)
Malformations of the respiratory tract	55 (1.7)
Malformations of the digestive system	362 (11.2)
Genital malformations	314 (9.8)
Malformations of the urinary tract	309 (9.6)
Malformations of the musculoskeletal system	668 (20.8)
Malformations of the limbs	184 (5.7)

Percentages do not add up to 100 % because children may have more than one malformation and therefore are counted in more than one malformation group

Information on congenital malformations is obtained from the medical files, including pathology reports, and coded afterwards, according to the International Classification of Diseases (ICD) coding system (until 2001: ICD 9th revison; from 2002: ICD 10th revision) by trained registry staff. Drugs that were taken by the mother are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [1, 13, 14].

From the EUROCAT NNL database we selected all foetuses and children (live births, stillbirths, spontaneous abortions and terminations of pregnancy) born between 1998 and 2008 ($n = 6{,}025$). We excluded cases without complete pharmacy records and without complete information regarding medication use ($n = 1{,}606$; 26.7 %). Because genetic and chromosomal disorders are not thought to be related to maternal medication use [15], cases with a genetic or chromosomal disorder ($n = 1{,}207$; 20.0 %) were also excluded. Our final dataset consisted of 3,212 cases. The cases were classified into different groups of malformations based on the ICD codes and the EUROCAT guidelines [16]. Table 1 shows the number of cases classified into the different malformation groups. Supplementary material 1 gives a list of all the malformations that are coded within the different malformation groups studied. If a child had multiple malformations, it was counted in all the categories represented ($n = 253$, 7.9 %), therefore numbers do not add up to 3,212. However, a child with several different cardiac malformations is only counted as one case within the groups of heart defects.

2.2 Population

From the IADB, a population-based prescription database that contains prescription data from approximately 55

community pharmacies in The Netherlands, we selected the population controls. The IADB covers an estimated population of 500,000 individuals, which is considered representative of the general population. Because most Dutch people only use one pharmacy, an almost complete medication history of each individual is registered in the database. Prescribed drugs are recorded by their Anatomical Therapeutic Chemical (ATC) code [14]. Data on date of dispensing, amount dispensed, dose regimen and the prescriber are also available. Each patient has a unique, anonymous identifier and his/her date of birth and gender are known. No information about medication prescribed during hospitalization or over-the-counter (OTC) drugs is available.

For the IADB pregnancy database, pregnancies are identified by connecting a child in the IADB to a female patient aged 15–50 years with the same address code as the child, providing there were no other female patients of this age with the same address code. This method allows 64.9 % of the mothers to be identified. Validation of this method has been described elsewhere [17]. The theoretical pregnancy period is defined by taking the date of birth of the child minus 273 days (three trimesters of 91 days). All 29,223 children, born from 28,528 pregnancies, with a date of birth between 1998 and 2008 were included in this study, including 1,320 twins and 56 multiple births.

2.3 Drugs

Because malformations develop in the first trimester of pregnancy [1], we focused on drug use and prescription use during this period. We defined the first trimester as the first 13 weeks of pregnancy. A case was defined to be exposed to one of the drugs under study when the drug was registered to be used during the first 13 weeks after the first day of the last menstrual period. For the population, the exposure definition was based on the date of prescription: if the mother received a prescription in the first 13 weeks of pregnancy, the child was considered exposed.

We selected two drug groups for our case-population study. The first group consisted of all drugs acting on the central nervous system (drugs with an ATC code starting with N). These types of drugs have been studied frequently and certain teratogenic effects have been identified, especially with the anti-epileptic drugs [5, 18–24]. A suitable method to detect signals of teratology should be able to detect known teratogenic effects.

The second group consisted of all drugs considered to be safe, classified as A (drugs that have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed) according to the Australian Drug Evaluation Committee (ADEC) [25], except drugs for fertility treatment. We did not expect any teratogenic effects to be found in this group.

The ATC classification is based on the organ system that a drug acts on and subsequently on its therapeutic and chemical characteristics, while the ADEC classification aims to classify risks associated with taking particular medicines in pregnancy based on the available evidence [13, 25]. The two drug groups under investigation were therefore composed differently. Because the IADB does not contain information on the use of OTC medication, only prescribed drugs were included.

2.4 Analyses

For the cases and population controls, mean maternal age and the distribution of the birth years over the study period were calculated and compared using the t-test and the Mann–Whitney U test, respectively.

From the EUROCAT NNL data, we calculated first trimester user rates among malformation groups as the percentage of cases exposed to a specific drug. To reduce the risk of chance findings, we calculated user rates only for drug groups and for specific drugs with at least three exposed cases in the first trimester. From the IADB data, we calculated prescription rates as the percentage of infants exposed in utero.

Because a drug usually acts on a certain organ system and causes specific birth defects, we did not compare the user rate among all malformations together with the IADB prescription rates. By taking all malformations together, any teratogenic effect would have been diluted and signals could have been missed.

The drug use rates among the malformation groups were compared with the IADB prescription rates by calculating rate ratios (RR) and 95 % confidence intervals (CIs). Analyses were performed using PASW Statistics, Version 18 (IBM, Chicago, IL, USA).

3 Results

Table 2 shows the distribution of the birth years of the cases and our population per study year. The number of births per year decreased over time for the population, because it can take some time before a pregnancy is identified in the IADB. The Mann–Whitney U test showed no significant difference ($p = 0.412$) between the distribution of the years of birth of the cases and of the IADB population in the study period. The mean age of the case mothers at birth was 30.4 years. The mean age of the population mothers at birth was 30.0 years. The t-test showed a significant difference ($p < 0.001$).

Table 2 Distribution of the birth years of the cases (EUROCAT NNL) and general population (IADB) per study year

Study year	EUROCAT NNL (n_{total} = 3,212)		IADB (n_{total} = 29,223)	
	n	%	*n*	%
1998	294	9.2	3,136	10.7
1999	303	9.4	3,353	11.5
2000	286	8.9	3,256	11.1
2001	273	8.5	3,105	10.6
2002	280	8.7	3,043	10.4
2003	320	10.0	2,887	9.9
2004	307	9.6	2,763	9.5
2005	305	9.5	2,419	8.3
2006	316	9.8	2,006	6.9
2007	260	8.1	1,740	6.0
2008	268	8.3	1,515	5.2

Table 3 shows the user rates (cases) and prescription rates (population) for the drugs investigated according to the malformation group. Based on our criterion of at least three exposed cases, seven specific drugs acting on the central nervous system and seven specific drugs considered to be safe were included in our analyses.

3.1 Drugs Acting on the Central Nervous System

Figure 1 shows the RRs for the drugs acting on the central nervous system that could be calculated for the malformation groups. The anti-epileptic drug valproic acid showed a significantly increased RR for heart anomalies of 5.98 (95 % CI 2.66–13.44) and for anomalies of the central nervous system of 15.05 (96 % CI 5.09–44.51). For some selective serotonin re-uptake inhibitors (SSRIs), we found certain significantly increased RRs: fluoxetine and anomalies of the digestive system: 3.73 (95 5 CI 1.23–11.32); citalopram and anomalies of the musculoskeletal system: 3.75 (96 % CI 1.26–11.14) and paroxetine and heart anomalies: 2.03 (95 % CI 1.14–3.62). The malformations observed can be found in Supplementary material 2.

We found no significantly increased RR for the anti-migraine drug sumatriptan or for the benzodiazepines, diazepam and oxazepam.

3.2 Drugs Considered To Be Safe

The RRs for specific drugs in the group of 'safe' drugs are shown in Fig. 2. The anti-hypertensive methyldopa showed significantly increased RRs for anomalies of the digestive system: 4.66 (96 % CI 1.54–14.06); genital anomalies: 5.37 (96 % CI 1.78–16.22) and urinary anomalies: 5.46 (95 % CI 1.81–16.49). The malformations observed can be found in supplementary material 2. We found no significantly increased RRs for metoclopramide, thyroxine, amoxicillin, nitrofurantoin, salbutamol or budesonide.

4 Discussion

In this case-population study, we investigated whether comparing drug use rates from a population-based birth defects registry with prescription rates from a population-based prescription database could be used as a suitable detection method for the teratogenic risk of drugs. For drugs acting on the central nervous system, we found significantly increased RRs for the anti-epileptic drug valproic acid and for some SSRIs. Of the drugs considered to be safe, only the anti-hypertensive methyldopa showed significantly increased RRs.

A suitable method for the detection of possible teratogenicity should be able to detect known teratogenic effects but should not detect any effects if a drug is considered to be safe. Based on the Bradford Hill criteria on causality [26], Meyboom et al. [27, 28] stated seven basic criteria for determining a signal. Of these criteria "quantitative strength of the association, consistency of the data, biological plausibility and experimental findings" can be applied to our study. A method to detect signals must pick up signals quickly and easily, and should therefore be easily applicable and relatively inexpensive. Although they have limitations, such as needing to control for potential confounders and quantifying the strength of the association found, case-population studies are considered to be useful for generating signals and testing hypotheses [11].

For the anti-epileptic drug valproic acid we found increased RRs for heart anomalies and for anomalies of the central nervous system. These results are in line with previous results [18, 19, 21, 22, 29]. The association between fluoxetine and anomalies of the digestive system was previously reported by Bakker et al. [30] using the same data from EUROCAT NNL. This association was confirmed by Colvin et al. [31].

Citalopram has been associated in the literature with neural tube defects [32] and septal heart defects [33] but we found no report of an association with musculoskeletal malformations. The association we found was based on three cases: two of them were affected by singular dysplasia of the hip, while the third case had a dysplasia and luxation of the hip. The broad confidence interval around the RR of 3.75 (95 % CI 1.26–11.14) indicates that this estimate is not very precise. As far as we know, this is the first report of such an association. There is no evidence of biological plausibility for the association of citalopram with hip anomalies. It should be noted that hip malformations are common in the northern Netherlands, with an

Table 3 User rates (cases) and prescription rates (general population) for the drugs investigated

	CASES—malformation categories[a] (n = 3,212)									Population (n = 29,223)
	Central nervous system (n = 208)	Heart (n = 873)	Clefts (n = 294)	Respiratory tract (n = 55)	Digestive system (n = 362)	Genitals (n = 314)	Urinary tract (n = 309)	Musculoskeletal (n = 668)	Limbs (n = 184)	
Drugs acting on nervous system (ATC code: N), n (%)										
Sumatriptan	0	4 (0.46)	0	0	0	0	<3[b]	0	0	58 (0.20)
Valproic acid	3 (0.01)	5 (0.57)	<3[b]	0	<3[b]	0	<3[b]	<3[b]	0	28 (0.09)
Diazepam	<3[b]	3 (0.34)	<3[b]	<3[b]	0	<3[b]	<3[b]	<3[b]	<3[b]	86 (0.29)
Oxazepam	<3[b]	3 (0.34)	<3[b]	<3[b]	3 (0.96)	<3[b]	<3[b]	3 (0.45)	0	161 (0.55)
Fluoxetine	<3[b]	3 (0.34)	<3[b]	0	3 (0.96)	0	0	<3[b]	0	65 (0.22)
Citalopram	0	0	0	0	<3[b]	0	0	3 (0.45)	0	35 (0.12)
Paroxetine	0	11 (1.26)	<3[a]	0	<3[b]	<3[b]	4 (1.29)	4 (0.60)	0	181 (0.62)
Drugs considered to be safe (ADEC classification: A), n (%)										
Metoclopramide	<3[b]	5 (0.57)	<3[b]	0	<3[b]	<3[b]	<3[b]	<3[b]	<3[b]	155 (0.53)
Methyldopa	0	0	0	0	3 (0.83)	3 (0.96)	3 (0.97)	<3[b]	0	52 (0.18)
Thyroxine	<3[b]	10 (1.15)	3 (1.02)	0	4 (1.10)	<3[b]	<3[b]	6 (0.90)	3 (1.63)	299 (1.02)
Amoxicillin	11 (5.29)	28 (3.21)	13 (4.42)	4 (7.27)	19 (5.25)	14 (4.46)	13 (4.21)	21 (3.14)	7 (3.80)	994 (3.40)
Nitrofurantoin	<3[b]	10 (1.15)	3 (1.02)	<3[b]	3 (0.83)	<3[b]	4 (1.29)	9 (1.35)	3 (1.63)	388 (1.33)
Salbutamol	5 (2.40)	8 (0.92)	3 (1.02)	<3[b]	7 (1.93)	8 (2.55)	6 (1.94)	13 (1.95)	5 (2.72)	426 (1.46)
Budesonide	0	5 (0.57)	<3[b]	<3[b]	<3[b]	<3[b]	<3[b]	<3[b]	<3[b]	83 (0.28)

ADEC Australian Drug Evaluation, *ATC* Anatomical Therapeutic Chemical Committee

[a] Children with multiple malformations were counted in multiple categories (n = 253, 7.9 %)

[b] Unequal to 0, but numbers too low to calculate a reliable RR

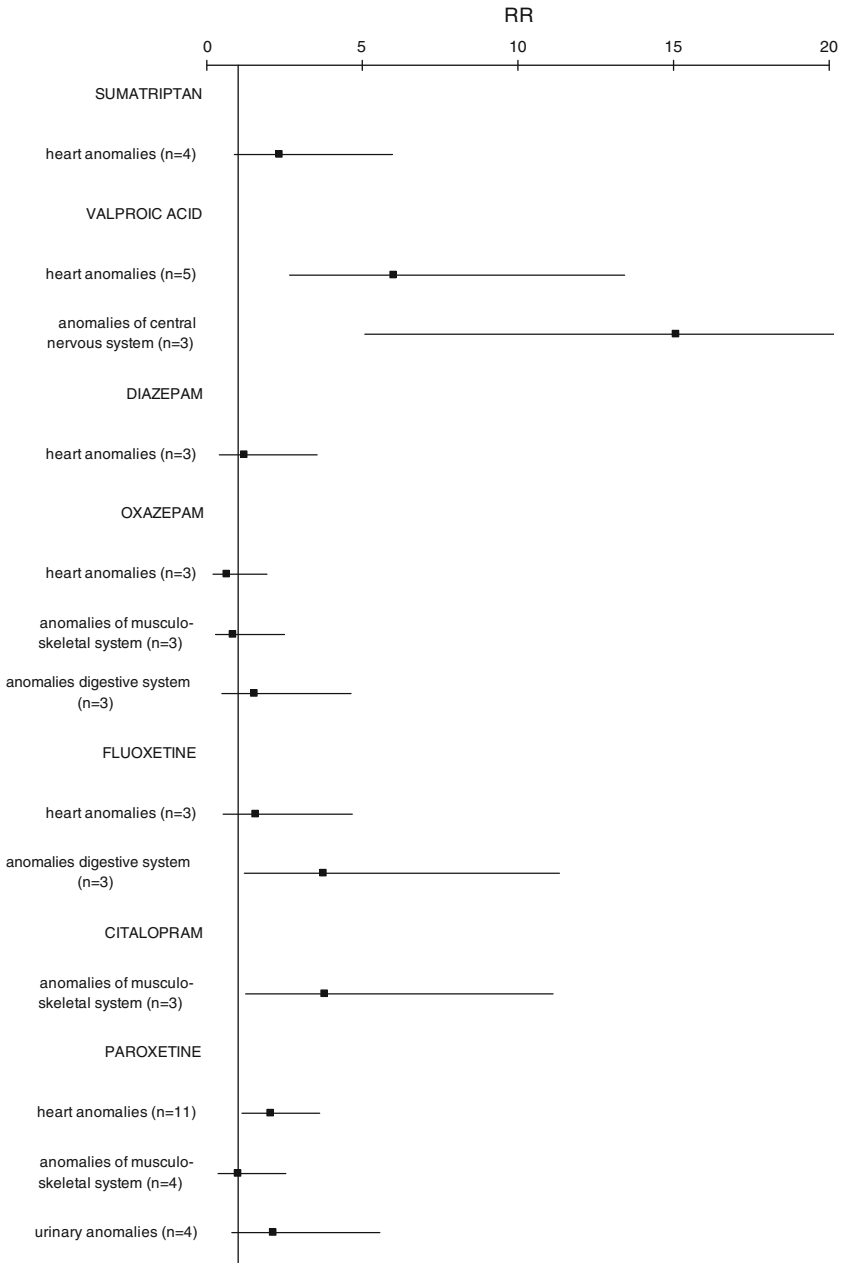

Fig. 1 Rate ratios (RR) calculated for drugs acting on the central nervous system for the different malformation groups

aetiology that was shown to be multi-factorial [34] and is unlikely to be drug induced. Our finding therefore needs further investigation in other datasets.

We found an increased RR for paroxetine and heart anomalies in general. The association between paroxetine and cardiac malformations, especially right ventricle outflow tract obstructions, has been reported by several other studies [33, 35, 36]. Using data from the same birth defect registry, EUROCAT NNL, a recent case-control study on first trimester use of paroxetine and congenital heart defects found a significantly increased risk for atrium septum defects but not for heart anomalies in general [37]. The association between paroxetine and cardiovascular malformation is still, however, a point of discussion. In his study of three meta-analyses on this topic, Scialli [38] states that by applying the Bradford Hill criteria of causality noted before, 'scientific evidence does not support for the conclusion that paroxetine causes cardiovascular defects'.

As expected, the RRs we found for the drugs considered to be safe were generally around one. However, significantly increased RRs were found for methyldopa and anomalies of the digestive system, genitals and urinary tract. One child contributed to all of these malformation groups. Because of low numbers this had a substantial effect on the RRs calculated, possibly leading to a false-

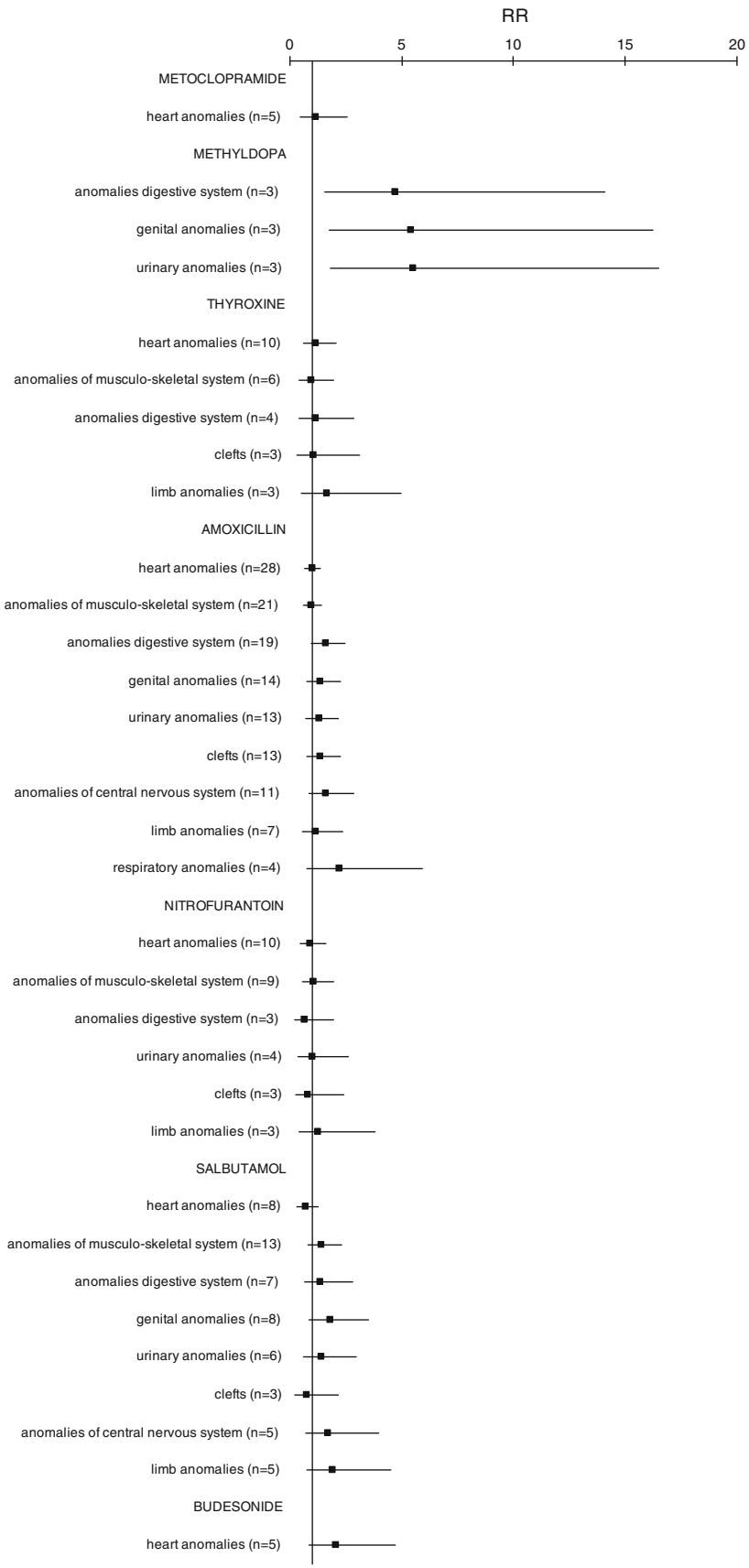

Fig. 2 Rate ratios (RR) calculated for drugs considered to be safe for the different malformation groups

positive signal. Furthermore, methyldopa is the most extensively used anti-hypertensive in pregnancy, because it is considered to be safe and efficient [39]. A number of studies have shown little difference in teratogenic risk between several anti-hypertensive medications and untreated hypertension, suggesting that the underlying hypertension itself might increase the risk for congenital malformations [40–43]. Additional studies are needed to elaborate on these findings.

4.1 Strengths and Limitations

Comparing data from EUROCAT NNL and IADB offers the opportunity to compare first-trimester drug exposure based on pharmacy data in two different databases, covering approximately the same geographical area and the same period. Because the data are available, the method is relatively easy and inexpensive. The IADB is a population-based, non-selected database, including a large number of pregnancies [17]. Almost complete records of prescription data are available because Dutch people normally only use one local pharmacy. For EUROCAT NNL, information about drug use is based on pharmacy records and verified in telephone interviews. The complementary use of pharmacy records and interview data provides the most complete medication history possible [44].

When using data from a prescription database, it is unknown whether the drug was actually taken, possibly leading to an overestimation of drug use. Olesen et al. [45] studied pregnant women's compliance in using prescribed drugs and found that it was high for drugs used to treat chronic diseases (70–100 %) but lower for short-term treatments. Another limitation is that because we only focused on the prescription date and not on the duration of the prescription, we will have missed drugs prescribed before the pregnancy, but used during pregnancy. The IADB only contains live births and has no information about congenital malformations, but because it is a population-based record, we expect about 3 % of the children to have a congenital anomaly [46]. These low numbers will only cause a minimal bias.

The actual gestational period of the pregnancies in the IADB is not known. Taking the theoretical gestation to determine first-trimester exposure may have led to some misclassifications. For more than one third of all children registered with the IADB a mother cannot be identified, possibly leading to selection bias. However, criteria for linking a child to a parent are very strict to avoid mismatching. Schirm et al. [17] demonstrate that more than 99 % of the coupled children were coupled to the right mother. For EUROCAT NNL, approximately 80 % of the parents agree with inclusion of their child in the registry. Women who agree with registration might differ from women who do not agree with regard to the type of anomaly or demographic factors, therefore selection bias cannot be excluded.

Only cases with complete pharmacy records and medication use were included. The cases excluded from the study population contained more miscarriages, terminated pregnancies and stillbirths than the cases with complete records and were relatively earlier in our study period. Malformations amongst stillbirths and terminations differ from malformations amongst live born, often being more serious and not compatible with life. Medications used might be different for these groups as well. Some bias may have occurred, which could have led to underestimation of medication use among cases and non-detection of some signals. However, this selection criterion was necessary to ensure the quality of our data.

We found a significant difference among the mean ages of the case and population mothers. In absolute terms, the difference is only of a small order, i.e. 0.4 years. Ideally, the results should be adjusted for age. However, because of small numbers adjustment was not possible.

Owing to the nature of the population data used, we were not able to adjust for potential confounding factors. Because we wanted to test a method for detecting signals quickly and easily, further studies designed to confirm or reject the signals we found should address the issue of confounders.

We could not detect associations described in the literature for several drugs acting on the central nervous system. Some of these associations, like the increased risk of clefts with exposure to diazepam, are controversial and literature reports are often inconsistent. We could only calculate RRs for a limited association between drugs and malformation groups because of small case groups and the incidental use of several drugs. Sample size calculations show that for the detection of a small risk (RR = 2) and an exposure of 0.2 % in the pregnant population, like for some of the drugs acting on the central nervous system we studied, approximately 7,100 cases would be needed. For a relatively common birth defect such as a heart defect (prevalence 0.7 %), this would cover about 1 million births. Larger databases are necessary to detect potential teratogenic effects of drugs not commonly used, from a large registration area with population data and also with information on drug use. This could probably be realized by adding other congenital anomaly registries with detailed information about drug use and the availability of population data.

5 Conclusions

This study was conducted to test the case-population approach for detecting signals, by comparing exposure rates between cases (from a birth defect register,

EUROCAT NNL) and the general population (represented by a pharmacy database, IADB). We show how this method was able to detect known teratogenic risks for several widely used drugs acting on the central nervous system. It did not detect any teratogenic effects for most drugs that are considered to be safe, assuming there were enough cases for a particularly anomaly. We can therefore assume that this is a suitable method for detecting signals of possible teratogenicity, providing that the teratogenic effects and drugs studied are as specific as possible, and the drugs are widely used.

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Conflict of interest L. de Jonge, P. A. Zetstra-van der Woude, H. J. Bos and M. K. Bakker have no conflicts of interest to disclose. LTW de Jong-van den Berg is a member of the advisory board of the H1N1 pregnancy study (funded by Novartis). The manuscript was edited by J.L. Senior, a full member of staff at the Department of Genetics, University Medical Center GroningenFro, Groningen, The Netherlands. The authors thank J. L. Senior for editorial assistance.

Contributions to authorship LdJ and PAZ-vdW were equally responsible for developing the study and method, statistical analysis, interpreting the findings and writing the manuscript. HJB was involved in the data collection and selection of the IADB section and contributed to all revisions of the manuscript. LTWdJ-vdB and MKB were responsible for developing the study and method, and supervising and contributing to all revisions of the manuscript.

Details of Ethics Approval Ethical approval was not necessary since only anonymous prescription data were used.

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