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REVIEW *Reproductive epidemiology*

Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks

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STUDY QUESTION: What is the current state of knowledge on the human risks of drugs suspected to be associated with teratogenic mechanisms?

SUMMARY ANSWER: Evidence for the presence or absence of human risks of birth defects is scarce or non-existent for the majority of drugs associated with teratogenic mechanisms.

WHAT IS KNOWN ALREADY: Medical drugs suspected to be associated with teratogenic mechanisms are dispensed to a significant proportion of women in the first trimester of pregnancy. However, an overview of the current state of knowledge on the human teratogenic effects of these drugs is lacking.

STUDY DESIGN, SIZE, DURATION: We performed an extensive literature review of studies in the English language which examined the associations between selected drugs and specific birth defects. The literature was identified from MEDLINE and EMBASE from database inception (January 1946 and January 1974, respectively) through December 2012 using 287 terms for the drugs of interest. We only included studies if they specified birth defect subtypes and, specifically for cohort studies, involved live born infants.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Of 14 406 potentially relevant articles, 556 full-text articles were assessed for eligibility and 250 met the inclusion criteria. The studies included were divided into four categories according to their design to increase the validity of our study.

MAIN RESULTS AND THE ROLE OF CHANCE: Epidemiologic studies assessing teratogenic risks were identified for less than half of the drugs included in the review. A substantial variation in study design and data collection methods was observed. When the data collection method is of questionable validity, study quality may be affected considerably. For only 15 drugs of interest, birth defects were assessed in at least 1000 infants in cohort studies, and 13 of these were associated with one or more specific birth defects. The majority of associations observed in case–control studies are as yet unconfirmed. For most drugs and drug groups, however, the numbers of exposed infants studied were too small to draw any conclusions regarding their human teratogenic risks.

LIMITATIONS, REASONS FOR CAUTION: The validity of our review is limited by the validity and reporting of the studies from which the data were extracted. Some relevant studies might have been missed owing to the exclusion of articles not in the English language and publication bias.

WIDER IMPLICATIONS OF THE FINDINGS: It is a cause of concern that the drugs most often dispensed in the first trimester of pregnancy are not necessarily the drugs for which teratogenic risks have been studied. Future studies should focus on those drugs that are most commonly used during pregnancy and for which the teratogenic risks are unknown, such as iron preparations, serotonin receptor agonists or antagonists, drugs used in fertility treatment, dihydrofolate reductase inhibitors.

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Introduction

In developed countries, prescription drug use is common during pregnancy with prevalence estimates ranging from 27 to 99%, depending on the data sources used and the types of medication included (Daw *et al.*, 2011). However, the human teratogenic risks are unknown for >90% of drug treatments approved for marketing in the USA since 1980 (Adam *et al.*, 2011). One of the reasons is that pregnant women are often excluded from participation in pre-marketing clinical trials. In addition, the results obtained from animal studies are not always predictive of a teratogenic effect in humans. Nevertheless, medication use is occasionally unavoidable in the treatment of women of reproductive age and during pregnancy, for instance among women with epilepsy, diabetes or severe hypertension.

A substantial number of medical drugs are suspected to induce birth defects through various mechanisms, including folate antagonism, vascular disruption and oxidative stress (van Gelder *et al.*, 2010). In a Dutch drug utilization study, 17.5% of women received one or more prescription drugs suspected to be associated with a teratogenic mechanism during the first trimester of pregnancy (van Gelder *et al.*, 2013a). However, it is unknown what the current state of knowledge on the human teratogenic risks of these particular drugs is. Therefore, we conducted an extensive literature review to assess the quantity of information available on the associations between these medications and specific birth defects. In addition, we evaluated a number of study design characteristics of the studies included in this review to assess their quality. Although a large part of the evidence in support of the suspected teratogenic mechanisms is derived from animal studies, research priorities may be defined by considering the results of studies determining which medications are most commonly used by pregnant women and this review of human data concurrently.

Materials and Methods

Search strategy

Our search strategy consisted of two stages. First, we searched the MEDLINE and EMBASE electronic databases from inception (January 1946 and January 1974, respectively) through December 2012. For the 287 individual drugs and therapeutic classes of interest as defined previously (van Gelder *et al.*, 2013a), we used MeSH terms for the generic names whenever applicable, focusing on adverse effects [ae] and toxicology [to]. These individual subsets were combined with the Boolean operator 'AND' with a subset that included terms for birth defects in general (congenital abnormalities; congenital disorder; birth defect) and a number of specific birth defects associated with the mechanisms studied (neural tube defects; congenital heart defects; cleft lip; cleft palate; congenital limb deformities; hypospadias; gastroschisis). Second, additional articles were identified from the reference lists of selected papers and from three books on teratogenic agents (Schaefer *et al.*, 2007; Shepard and Lemire, 2007; Briggs *et al.*, 2011).

Study selection

We selected English-language studies that examined the association between the drugs of interest and major birth defects in humans. The studies included were divided into four categories according to their study design: population-based cohort studies, cohort studies using data from voluntary pregnancy exposure registries (register-based cohort studies), case–control studies using population controls and case–control studies using malformed control subjects. The single RCT included was classified as a population-based cohort study. Cohort studies were only included if they prospectively collected information on medication use before the outcome of the pregnancy was known. Case–control studies with less than 100 cases were excluded because of power limitations, as well as case–control studies in which self-reported data were collected >2 years after delivery which leads to a lack of validity regarding medication use (van Gelder *et al.*, 2013b).

Articles were excluded from the review if they did not specify the drug under study (e.g. studies on any antidepressant) or if drug exposure did not pertain to the first trimester of pregnancy. Although the aetiologically relevant time period for all birth defects considered in this review includes the first 4 months of pregnancy (up to and including week 14 after conception), the first trimester is often the only time period for which exposure was reported in the selected papers. Results from studies on associations between antiepileptic drugs and birth defects were only included if monotherapy was used because the teratogenic risks of antiepileptic drug polytherapies, especially those that include valproic acid, are higher compared with monotherapy only (Holmes *et al.*, 2011).

Since birth defects as a group are a very heterogeneous collection of disorders with each specific defect having its own set of risk factors, they should not be considered as a single outcome (Wilcox, 2010a). Therefore, we only included studies if they specified birth defect subtypes. In addition, we only included live born infants from cohort studies as the diagnostic specificity of defects in miscarriages, stillbirths and terminations of pregnancy varied greatly between the different studies. All infants with malformations were classified according to the 64 standard EUROCAT birth defect subgroups (EUROCAT, 2005). Because of coding and reporting issues (e.g. classification dependent on gestational age or severity of the defect, defects for which the congenital nature may be questionable, or defects that are often poorly specified), we excluded hydrocephalus, microcephaly, hypoplastic right heart, patent ductus arteriosus, cystic adenomatous malformations of the lung, renal anomalies, indeterminate sex, clubfoot, hip dislocation, skeletal dysplasias, amniotic bands and skin disorders. Furthermore, known or suspected genetic syndromes, microdeletions and chromosomal abnormalities were excluded.

Owing to the size of the literature search, only one reviewer (M.v.G.) screened the titles and abstracts of all identified citations. Subsequently, the full-text articles of all publications that were likely to meet the inclusion criteria were obtained and reviewed, leading to a final decision on inclusion or exclusion. In case of doubt, eligibility was discussed with the two senior authors (L.d.J.v.d.B. and N.R.).

Data extraction and analysis

To get more insight into the quality of the studies included, we considered the following study design characteristics: inclusion of an unexposed reference population (for cohort studies), follow-up rates for exposed and unexposed subjects (for cohort studies), participation rates (for case–control studies) and methods of data collection used for exposure and outcome assessment (for all studies).

For each study included, we extracted the outcome data in 2 × 2 tables, as well as the crude and adjusted measures of effect with their confidence intervals for the associations between the drugs of interest and specific birth defects. When the studies did not report the crude effect, this measure was calculated from the raw data abstracted. Based on the cohort studies included, the prevalence of each birth defect among live born infants

exposed to a specific drug during development was calculated by dividing the total number of cases from the different studies by the total number of live born infants exposed to the drug. As hypospadias only occurs in boys, we assumed that the proportion of boys was 0.51 among live births to calculate the number of exposed infants at risk for this birth defect (Wilcox, 2010b). The prevalence was only calculated if there were at least three cases or at least 1000 exposed infants, since the current guidelines of the European Medicines Agency require pharmaceutical companies to prospectively collect at least 1000 exposed pregnancies to reach the conclusion that the drug is not responsible for a 2-fold increase in the overall occurrence of congenital malformations (Committee for Medicinal Products for Human Use, 2008). The prevalence observed was compared with prevalence estimates for the specific defect among live born infants in Europe and the USA (Anonymous, 2007; EUROCAT Central Registry, 2008) using Yates' corrected chi-square tests as described by Jentink *et al.*, (2010a), because a substantial number of cohort studies did not include an unexposed reference population or the reference population was too small to draw any conclusion. The statistical analyses were performed using the Statistical Package for the Social Sciences version 20 for Windows (IBM Corp., Armonk, NY, USA). A $P < 0.05$ was considered statistically significant.

Results

Search results

The search strategy identified 14 406 citations, of which 14 300 were captured from electronic databases and 106 were retrieved by hand-searching (Fig. 1). Of these, 556 original research articles were eligible for a full-text review. A total of 306 studies were excluded because they did not meet the inclusion criteria; therefore, we assessed 250 studies. Of these, 115 reported on population-based cohort studies, 64 reported the results of register-based cohort studies, 58 reported case–control studies with population controls and 18 reported case–control studies with malformed controls. A total of five case–control studies used both population and malformed control groups and were

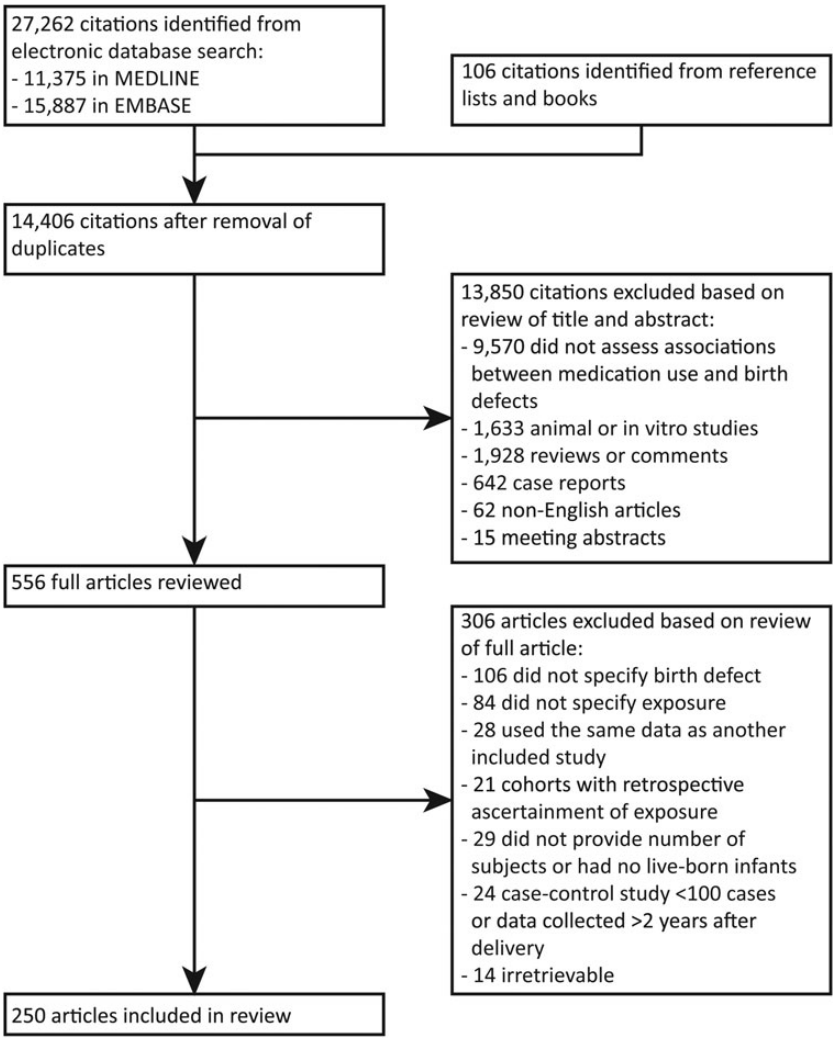

Figure 1 Review and selection of articles in the literature review.

included in both categories. The references of the included studies are provided in Supplementary Data.

Study design characteristics

A total of 65 (56.5%) population-based cohorts and 35 (54.7%) register-based cohort studies included an unexposed reference population. The follow-up rates for exposed subjects in population-based cohorts were reported in only four (3.5%) publications, ranging between 70.3% and 100%. In contrast, 26 (40.6%) register-based cohort studies reported follow-up rates for exposed subjects (range: 35.4–94.8%). The participation rates in case–control studies with population controls were reported in 34 (58.6%) publications for cases (range: 65.0–97.1%) and in 33 (56.9%) publications for control subjects (range: 64.0–83.0%). In case–control studies with malformed controls, participation rates were reported in seven (38.9%) publications, ranging between 80.0% and 97.0% for both cases and controls.

The methods of data collection used in the studies included are shown in Table I. More than 12% of the cohort studies did not report on their modes of data collection, while this applied to only two case–control studies. Regarding exposure assessment, population-based cohorts most often relied on medical records (47.8%), while in the other three study design categories, self-reported methods (i.e. interviews or self-administered questionnaires) were predominantly used (62.5–84.5%). In 32 studies, these data were complemented with medication details from medical records. For data on the diagnosis of birth defects, most studies relied on registries or medical records. However, 54.7% of register-based cohorts collected these data through maternal self-report. Nineteen of these studies also reviewed medical records, but only from infants whose mothers reported a birth defect.

Drugs studied in relation to birth defects

Results were included from a total of 103 and 59 drugs or drug groups from cohort studies and case–control studies, respectively. Table II shows the numbers of cohort studies and exposed infants that contributed to the prevalence estimates for individual drugs. The drugs with the largest number of infants studied in relation to birth defects in population-based cohorts were acetaminophen, selective serotonin-reuptake inhibitors (SSRIs), aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and progesterone. The four drugs studied most often were all antiepileptic drugs: phenytoin, carbamazepine, phenobarbital and valproic acid. In the register-based cohorts, most infants were exposed to lamotrigine, carbamazepine, valproic acid and fluoxetine. In four studies, isotretinoin was the exposure of interest, but these studies contained a total of only 60 live born infants. For many other drugs or drug groups, very small numbers of infants were included in cohort studies.

The numbers of case–control studies and cases included for specific drugs are given in Table III. For eight drugs or drug groups, exposure was assessed in more than 10 000 cases with population controls: clomiphene, aspirin, oral contraceptives, acetaminophen, naproxen, ibuprofen, SSRIs and promethazine. The teratogenic potential of antihypertensive medication was investigated in four studies with a total of 6858 cases. The other drugs and drug groups were included in less than four case–control studies with population controls, while case–control studies with malformed controls were only rarely conducted. The drugs most

Table I Methods of data collection used to assess exposure and outcome in the human studies included in the literature review of medication use and birth defects.

Study design	No. of studies[a]	Exposure assessment (%)					Outcome assessment (%)				
		Registry	Medical records	Self-report	Other	Not reported	Registry	Medical records	Physical examination	Self-report	Not reported
Population-based cohort	115	23.5	47.8	14.8	2.6	13.0	24.3	39.1	20.9	4.3	13.0
Register-based cohort	64	0	26.6	62.5	0	17.2	0	62.5	7.8	54.7	12.5
Case–control, population controls	58	5.2	39.7	84.5	0	3.4	50.0	46.6	1.7	0	1.7
Case–control, malformed controls	18	0	55.6	77.8	16.7	0	33.3	66.7	0	0	0

Percentages do not add up to 100% as in some studies as multiple methods of data collection were used.
[a]Five case–control studies used both population and malformed control groups and were included in both case–control categories.

Table II Summary of the cohort studies included in the literature review of human medication use and birth defects.

Drug	Mechanism	Population-based cohorts		Register-based cohorts	
		No. of studies	No. of exp. infants	No. of studies	No. of exp. infants
5-Fluorouracil	OS	1	4	0	0
Acetaminophen	OS	3	26 663[a]	2	66
Acetazolamide	CA	0	0	1	1
Amiodarone	OS	2	6	0	0
Amitriptyline	5-HT	0	0	1	89
Antihypertensive medication	VD	1	1430	1	400
ACE inhibitor/AT II blocker	VD + AT	0	0	1	188
ACE inhibitor	VD + AT	2	268	1	8
Captopril	VD + AT	1	9	1	15
Enalapril	VD + AT	1	9	1	6
Lisinopril	VD + AT	1	9	0	0
AT II blocker	VD + AT	3	30	1	30
Acebutolol	VD	1	6	0	0
Atenolol	VD	1	5	0	0
Calcium channel blocker	VD	1	25	2	293
Amlodipine	VD	0	0	1	31
Diltiazem	VD	0	0	1	29
Felodipine	VD	1	3	0	0
Nifedipine	OS + VD	0	0	1	51
Verapamil	VD	0	0	1	55
Pindolol	VD	1	7	0	0
Sotalol	VD	1	1	0	0
Benzodiazepines	OS + GA	2	1397[a]	2	459
Alprazolam	OS + GA	1	6	1	276
Chlordiazepoxide	OS + GA	1	18	0	0
Clobazam	OS + GA	0	0	1	9
Clonazepam	OS + GA	3	45	1	9
Diazepam	OS + GA	2	38	0	0
Lorazepam	OS + GA	1	1	0	0
Bromocriptine	5-HT	0	0	1	375
Cabergoline	5-HT	2	173	1	49
Carbamazapine	FA	12	1370[a]	4	1528[a]
Chlorpromazine	OS	1	57	0	0
Cisapride	5-HT	0	0	1	88
Clomipramine	5-HT	1	1029[a]	1	87
Cyclosporine	FA	2	63	0	0
Doxepin	5-HT	0	0	1	8
Ergotamine	VD	1	213	0	0
Imipramine	5-HT	0	0	1	27
Isoniazid	OS	1	17	0	0
Isotretinoin	NC	0	0	4	60[a]
Lamotrigine	FA	2	135	4	3518[a]
Maprotiline	5-HT	0	0	1	77
Mercaptopurine	OS	2	11	0	0
Metformin	FA	3	327	0	0
Methotrexate	FA + OS	2	7	2	20

Continued

Table II *Continued*

Drug	Mechanism	Population-based cohorts		Register-based cohorts	
		No. of studies	No. of exp. infants	No. of studies	No. of exp. infants
Metoclopramide	5-HT	1	189	1	158
Metronidazole	OS	3	102	1	131
Mianserin	5-HT	1	63	1	37
Mirtazapine	5-HT	1	154	2	75
Misoprostol	VD	1	118	1	67
Naratriptan	VD + 5-HT	0	0	1	46
Nitrofurantoin	OS	1	32	0	0
NSAIDs	VD + CI	2	5560[a]	0	0
Diclofenac	VD + CI	0	0	1	123
Ibuprofen	VD + CI	0	0	1	22
Tiaprofenic acid	VD + CI	0	0	1	7
Nortriptyline	5-HT	0	0	1	4
Olanzapine	5-HT	0	0	1	18
Ondansetron	5-HT	1	10	1	169
Oxomemazine	OS	1	14	0	0
Phenobarbital	FA + OS + GA	10	1815[a]	2	294[a]
Phenytoin	FA + OS	12	501[a]	1	17
Pizotifen	5-HT	1	12	0	0
Primidone	FA + GA	4	86[a]	0	0
Promethazine	OS	2	2775[a]	1	13
Pyrimethamine	FA	0	0	1	149
Rizatriptan	VD + 5-HT	0	0	1	23
Salbutamol	VD	1	648[a]	0	0
Salicylates	HI	1	146	0	0
Aspirin	OS + HI + CI	2	16 091[a]	0	0
Sex hormones	ED	2	1235	0	0
17-Hydroxyprogesterone	ED	1	140	0	0
Allylestrenol	ED	1	27	0	0
Clomiphene	ED	6	1711	0	0
Corifollitropin alfa	ED	1	806	0	0
Diethylstilbestrol	ED	2	1053[a]	0	0
Human chorionic gonadotrophin	ED	2	345	0	0
Hormonal pregnancy test	ED	1	661	0	0
Oral contraceptives	ED	2	1200[a]	1	99
DMPA	ED	1	15	0	0
Levonorgestrel	ED	1	272	0	0
Progesterone	ED	8	4306[a]	0	0
Recombinant FSH	ED	1	370	0	0
Stilbestrol	ED	1	2	0	0
SSRIs	5-HT	5	17 408[a]	3	380
Citalopram	5-HT	4	2078[a]	1	184
Escitalopram	5-HT	2	300[a]	1	21
Fluoxetine	5-HT	3	2581[a]	5	643
Fluvoxamine	5-HT	0	0	2	102
Paroxetine	5-HT	5	3449[a]	3	499
Sertraline	5-HT	4	4305[a]	1	61

Continued

Table II *Continued*

Drug	Mechanism	Population-based cohorts		Register-based cohorts	
		No. of studies	No. of exp. infants	No. of studies	No. of exp. infants
Statins	HMG	1	61	3	264
Sulfasalazine	FA	1	40	0	0
Sumatriptan	VD + 5-HT	2	725	2	544
Tetracycline	OS	1	341[a]	0	0
Thalidomide	OS	1	5	0	0
Topiramate	CA	2	877	2	103
Trazodone	5-HT	0	0	2	27
Tretinoin	NC	1	212	2	177
Valproic acid	FA + OS + HI	10	492[a]	5	1345[a]
Vitamin A	NC	0	0	1	311
Zidovudine	OS	2	358[a]	2	58

5-HT, influence serotonin signaling; ACE, angiotensin-converting enzyme; AT, disturb angiotensin–renin system; AT II, angiotensin II; CA, carbonic anhydrase inhibition; CI, cyclo-oxygenase inhibition; DMPA, depot medroxyprogesterone acetate; ED, endocrine disruption; FA, folate antagonism; GA, GABA receptor antagonist; HI, HDAC inhibition; HMG, HMG-CoA reductase inhibition; NC, neural crest cell disruption; NSAID, non-steroidal anti-inflammatory drug; OS, oxidative stress; SSRI, selective serotonin-reuptake inhibitor; VD, vascular disruption.
[a]Not all specific birth defects were assessed in all live born infants.

often assessed in these studies were valproic acid, carbamazepine, diazepam, promethazine and oral contraceptives.

Risk assessment

For 13 of the 15 (86.7%) drugs of interest with at least 1000 exposed infants in which selected defects were assessed in cohort studies, largely increased prevalence rates were observed for one or more specific birth defects. We detected 30 statistically significant associations between the drugs of interest and specific birth defects when we compared the prevalence rates with both reference populations for acetaminophen, antihypertensive medication, aspirin, phenobarbital, sex hormones, clomiphene, progesterone, SSRIs, citalopram, fluoxetine, paroxetine, sertraline and valproic acid (Table IV). Only for NSAIDs and lamotrigine, increased risks of specific birth defects were not observed compared with both reference populations. However, based on the population-based cohorts, NSAIDs seemed to be associated with ventricular septal defects (prevalence 52.16 per 10 000, $P < 0.001$ for European and $P = 0.07$ for US controls) and atrial septal defects (30.58 per 10 000, $P = 0.09$ for European and $P < 0.001$ for US controls)(Ericson and Källén, 2001; van Gelder *et al.*, 2011). Based on the register-based cohorts, lamotrigine seemed to increase the risk of cleft palate (17.40 per 10 000, $P = 0.03$ for European and $P = 0.05$ for US controls)(Vajda *et al.*, 2006; Holmes *et al.*, 2008; Cunnington *et al.*, 2011). In Supplementary Table SI, the statistically significant associations between drugs studied in less than 1000 exposed infants and specific birth defects are shown. The drugs involved include angiotensin-converting enzyme inhibitors, carbamazepine, isotretinoin, ondansetron, salicylates, corifollitropin alpha, hormonal pregnancy tests, recombinant FSH, statins, tetracycline, topiramate and zidovudine, as well as fluoxetine, sertraline, sex hormones and valproic acid that are also included in Table IV.

A total of 18 drug-birth defect associations observed in a case–control study were confirmed in at least one other study (Table V), including increased risks after prenatal exposure to acetaminophen, antihypertensive medication, clomiphene, fluoxetine, naproxen, NSAIDs, oxprenolol, phenytoin, progestin/progesterone, SSRIs and valproic acid. In addition, 22 associations were not studied by others or only in cohort studies with less than 1000 exposed infants, while 25 observed associations were refuted by others (Supplementary Table SII). As conclusions from a single study remain provisional, replication is crucial to enable risk assessment based on case–control studies. Interestingly, all case–control studies that assessed associations between oral contraceptives and limb reduction defects ($n = 4$) or hypospadias ($n = 5$) did not find increased risks (Janerich *et al.*, 1974; Hill *et al.*, 1988; Källén *et al.*, 1991; Czeizel and Kodaj, 1995; Wogelius *et al.*, 2006; Nørgaard *et al.*, 2009; Waller *et al.*, 2010).

Discussion

This study aimed to obtain more insight into the quantity of information available on the associations between drugs linked to a teratogenic mechanism and the risk of specific birth defects. Epidemiologic studies that assessed these teratogenic risks were identified for less than half of the drugs included. For only 15 drugs of interest, specific birth defects were assessed in at least 1000 infants in cohort studies and increased risks were found. The majority of associations observed in case–control studies are as yet unconfirmed; they were either not studied or refuted by others. For most drugs and drug groups, the numbers of exposed infants were too small to draw any conclusions regarding their human teratogenic risks.

Study strengths and limitations

Despite our exhaustive search strategies in this literature review, some potentially relevant studies might have been missed due to the exclusion of non-English-language articles and publication bias. In addition, our focus on the risks of specific birth defects instead of the overall

Table III Summary of the case–control studies included in the literature review of human medication use and birth defects.

Drug	Mechanism	Case–control studies with population controls		Case–control studies with malformed controls	
		No. of studies	No. of cases	No. of studies	No. of cases
Acetaminophen	OS	5	14 153	3	1822
Antihypertensive medication	VD	4	6858	0	0
ACE inhibitor	VD + AT	1	758	0	0
AT II blocker	VD + AT	1	758	0	0
Atenolol	VD	1	758	0	0
Calcium channel blocker	VD	2	6175	0	0
Furosemide	VD	1	2958	0	0
Methyldopa	VD	1	758	0	0
Metoprolol	VD	1	601	0	0
Oxprenolol	VD	1	1975	1	1374
Propranolol	VD	1	1769	0	0
Benzodiazepines	OS + GA	1	1044	1	826
Chlordiazepoxide	OS + GA	3	6791	0	0
Diazepam	OS + GA	3	6960	3	3703
Nitrazepam	OS + GA	1	809	0	0
Oxazepam	OS + GA	0	0	1	277
Carbamazepine	FA	1	601	1	11 872
Dextromethorphan	NA	2	1494	1	332
Doxycycline	OS	1	3405	0	0
Ephedrine	VD	1	381	0	0
Epinephrine	VD	1	381	0	0
Lamotrigine	FA	0	0	1	1943
Metoclopramide	5-HT	1	2098	0	0
Metronidazole	OS	2	6924	1	1374
Misoprostol	VD	1	452	0	0
Nitrofurantoin	OS	2	5810	1	1374
NSAIDs	VD + CI	5	2391	0	0
Ibuprofen	VD + CI	4	11 917	1	332
Naproxen	VD + CI	3	12 396	0	0
Ondansetron	5-HT	1	2797	0	0
Oxytetracycline	OS	2	5359	0	0
Phenobarbital	FA + GA	1	1975	1	1374
Phenytoin	FA	1	1374	1	1374
Promethazine	OS	3	13 833	1	3094
Salbutamol	VD	2	3010	1	294
Salicylates	HI	2	487	1	327
Aspirin	OS + HI + CI	9	19 050	4	2640
Salmeterol	VD	1	381	0	0
Sex hormones	ED	3	1069	2	932
17-hydroxyprogesterone	ED	3	5898	1	1374
Allylestrenol	ED	1	1975	1	1374
Fertility treatment	ED	3	1943	0	0
Clomiphene	ED	5	21 024	2	973
Human chorionic gonadotrophin	ED	1	4960	2	1699
Progestin	ED	1	500	0	0

Continued

Table III *Continued*

Drug	Mechanism	Case–control studies with population controls		Case–control studies with malformed controls	
		No. of studies	No. of cases	No. of studies	No. of cases
Hormonal pregnancy test	ED	2	371	0	0
Oral contraceptives	ED	8	15 994	1	3038
Estrogen	ED	2	381	0	0
SSRIs	5-HT	2	11 171	0	0
Citalopram	5-HT	1	1923	0	0
Fluoxetine	5-HT	2	6728	0	0
Paroxetine	5-HT	2	6728	1	183
Sertraline	5-HT	2	6728	0	0
Sulfasalazine	FA	2	2413	0	0
Terbutaline	OS + VD	1	1975	1	1374
Triptans	VD	1	514	0	0
Valproic acid	FA + OS + HI	1	2375	2	36 709
Vitamin A	NC	0	0	1	542

5-HT, influence serotonin signaling; ACE, angiotensin-converting enzyme; AT, disturb angiotensin-renin system; CI, cyclo-oxygenase inhibition; ED, endocrine disruption; FA, folate antagonism; GA,GABAreceptor antagonist; HI, HDAC inhibitor; NA, NSAID, non-steroidal anti-inflammatory drug; NA. NMDA receptor antagonism (NMDA, N-metthly-D-aspartate); OS, oxidative stress; SSRI, selective serotonin-reuptake inhibitor; VD, vascular disruption.

occurrence of congenital malformations led to the exclusion of 106 papers. In these studies, increased risks of birth defects overall may or may not have been found, but increases in the prevalence of specific birth defects were not addressed and could easily have been missed. The same argument applies to restricting the exposure to specific medical drugs. As a result, a small number of papers that combined certain drugs into one exposure variable based on their proposed teratogenic mechanism (e.g. folate antagonism; Hernández-Díaz *et al.*, 2000; 2001; Meijer *et al.*, 2005) were not included. The decision to exclude case reports and case series resulted in excluding the landmark papers that identified the teratogenic properties of thalidomide and isotretinoin (McBride, 1961; Lenz, 1962; Lammer *et al.*, 1985). Furthermore, heterogeneity within the birth defect groups may have masked associations between medication use and certain birth defects. To decrease this aetiological and phenotypical heterogeneity, we excluded a number of defects. In addition, we only included live born infants as the diagnostic specificity of defects in miscarriages, stillbirths and terminations of pregnancy varied greatly between different studies.

As with all literature reviews, the validity of the results is limited by the validity and reporting of the studies from which the original data were extracted. To increase the validity of our study, we divided the studies that were included into four study design categories. As register-based cohort studies are prone to selection bias (Martínez-Frías and Rodríguez-Pinilla, 1999; Johnson *et al.*, 2001), the results from these studies were separated from those of population-based cohort studies. Comparatively, case–control studies with population controls (prone to recall bias) were separated from those with malformed control subjects (prone to selection bias). For the cohort studies, this approach decreased the study power to detect increased prevalence of specific birth defects associated with the drugs and drug groups selected. However, as the case–control studies were not pooled, our approach did not affect the ability to detect associations in epidemiologic studies with this design.

Implications

Overall, the numbers of subjects included in epidemiologic studies on the teratogenicity of drugs associated with a teratogenic mechanism were small. For only 15 drugs or drug groups, more than 1000 exposed live born infants were included in either population-based or register-based cohort studies. For 13 of these, including acetaminophen and aspirin, which are available over-the-counter as well, increased risks with one or more specific birth defects were observed. As the current European guidelines for risk assessment only focus on the overall occurrence of birth defects, associations with specific birth defects may be missed, leading to the premature conclusion that a pharmacological treatment is safe for the developing fetus. However, the absolute risks are very small and not treating certain illnesses during pregnancy may endanger both maternal and fetal health.

The study design characteristics of epidemiologic studies on the teratogenic effects of medication use during pregnancy may raise some concern. Only a small majority of the cohort studies included a reference group of pregnancies unexposed to the drug of interest. Using an internal reference group, however, does not guarantee meaningful and valid comparisons due to lack of statistical power and the frequently present inability to correct for confounding by indication, which is an issue affecting many studies in pharmacoepidemiology (Csizmadi *et al.*, 2005). Not reporting participation or follow-up rates, which was the case in 72% of the studies included, may feed scepticism about the results, although selective participation in birth cohort studies does not seem to influence exposure–outcome associations (Nohr *et al.*, 2006; Nilsen *et al.*, 2009). In addition, the method of data collection used may affect the

Table IV Overview of the associations that were statistically significant when compared with the European and US reference populations between drugs of interest and specific birth defects that were assessed in at least 1000 exposed live born infants in cohort studies.[a]

Drug	Birth defect	Number of infants			Reference population				Reference
					Europe		USA		
		Exposed	Affected	Prev.	Prev.	*P*-value	Prev.	*P*-value	
Acetaminophen	Cleft palate	26 479	44	16.62	4.90	<0.001	5.45	<0.001	Thulstrup *et al.* (1999), Rebordosa *et al.* (2008)
Acetaminophen	Craniosynostosis	26 479	33	12.46	1.12	<0.001	3.90	<0.001	Thulstrup *et al.* (1999), Rebordosa *et al.* (2008)
Acetaminophen	Hirschsprung's disease	26 479	15	5.66	1.03	<0.001	1.84	<0.001	Thulstrup *et al.* (1999), Rebordosa *et al.* (2008)
Antihypertensive	Aortic valve atresia/stenosis	1430	3	20.98	1.00	<0.001	1.10	<0.001	Lennestål *et al.* (2009)
Antihypertensive	ASD	1430	12	83.92	19.48	<0.001	8.37	<0.001	Lennestål *et al.* (2009)
Antihypertensive	Coarctation of aorta	1430	3	20.98	2.96	0.001	3.88	0.002	Lennestål *et al.* (2009)
Antihypertensive	Hypoplastic left heart	1430	3	20.98	1.34	<0.001	2.51	<0.001	Lennestål *et al.* (2009)
Antihypertensive	VSD	1430	22	153.85	26.35	<0.001	36.67	<0.001	Lennestål *et al.* (2009)
Aspirin	Anorectal malformation	14 864	13	8.75	2.22	<0.001	3.71	0.003	Heinonen *et al.* (1977)
Aspirin	Aortic valve atresia/stenosis	14 864	8	5.38	1.00	<0.001	1.10	<0.001	Heinonen *et al.* (1977)
Aspirin	Cataract	14 864	17	11.44	1.06	<0.001	2.15	<0.001	Heinonen *et al.* (1977)
Aspirin	Coarctation of aorta	14 864	17	11.44	2.96	<0.001	3.88	<0.001	Heinonen *et al.* (1977)
Aspirin	Omphalocele	14 864	10	6.73	1.16	<0.001	2.73	0.008	Heinonen *et al.* (1977)
Aspirin	Polydactyly	14 864	116	78.04	7.23	<0.001	15.53	<0.001	Heinonen *et al.* (1977)
Aspirin	Spina bifida	14 864	19	12.78	1.99	<0.001	5.73	0.001	Heinonen *et al.* (1977)
Phenobarbital	Coarctation of aorta	1787	4	22.38	2.96	<0.001	3.88	0.001	Fedrick (1973), Lowe (1973), Heinonen *et al.* (1977), Bertollini *et al.* (1987), Kaneko *et al.* (1988), Waters *et al.* (1994), Canger *et al.* (1999), Holmes *et al.* (2001), Timmermann *et al.* (2009)
Phenobarbital	Polydactyly	1815	13	71.63	7.23	<0.001	15.53	<0.001	Fedrick (1973), Lowe (1973), Annegers *et al.* (1974), Heinonen *et al.* (1977), Bertollini *et al.* (1987), Kaneko *et al.* (1988), Waters *et al.* (1994), Canger *et al.* (1999), Holmes *et al.* (2001), Timmermann *et al.* (2009)
Sex hormones	Aortic valve atresia/stenosis	1235	4	32.39	1.00	<0.001	1.10	<0.001	Heinonen *et al.* (1977), Dal Pizzol *et al.* (2008)
Clomiphene	Cleft palate	1711	4	23.38	1.88	0.004	2.16	0.008	Hack *et al.* (1972), Ahlgren *et al.* (1976), Gorlitsky *et al.* (1978), Correy *et al.* (1982), Kurachi *et al.* (1983), Tulandi *et al.* (2006)
Clomiphene	Polydactyly	1711	8	46.76	7.23	<0.001	15.53	0.003	Hack *et al.* (1972), Ahlgren *et al.* (1976), Gorlitsky *et al.* (1978), Correy *et al.* (1982), Kurachi *et al.* (1983), Tulandi *et al.* (2006)

Continued

Table IV *Continued*

Drug	Birth defect	Number of infants			Reference population				
					Europe		USA		Reference
		Exposed	Affected	Prev.	Prev.	*P*-value	Prev.	*P*-value	
Progesterone	Hypospadias	2683	35	126.72	26.06	<0.001	59.35	<0.001	Dillon (1970), Harlap *et al.* (1975), Mau (1981), Katz *et al.* (1985), Resseguie *et al.* (1985), Rock *et al.* (1985), Yovich *et al.* (1988), Colvin *et al.* (2010)
SSRIs	ASD	9868	47	47.63	19.48	<0.001	8.37	<0.001	Oberlander *et al.* (2008), Colvin *et al.* (2011), Jimenez-Solem *et al.* (2012)
SSRIs	Small intestinal atresia	6555	4	6.10	0.58	<0.001	1.63	0.02	Källén and Otterblad Olausson (2007)
Citalopram	ASD	1993	12	60.21	19.48	<0.001	8.37	<0.001	Ericson *et al.* (1999), Heikkinen *et al.* (2002), Jimenez-Solem *et al.* (2012)
Fluoxetine	ASD	2447	13	53.13	19.48	<0.001	8.37	<0.001	Reis and Källén (2010), Jimenez-Solem *et al.* (2012)
Paroxetine	ASD	2796	14	50.07	19.48	0.001	8.37	<0.001	Cole *et al.* (2007), Reis and Källén (2010), Jimenez-Solem *et al.* (2012)
Paroxetine	Pulmonary valve stenosis	1020	4	39.22	3.15	<0.001	4.18	<0.001	Cole *et al.* (2007)
Paroxetine	VSD	2907	21	72.24	26.35	<0.001	36.67	0.003	Cole *et al.* (2007), Wichman *et al.* (2009), Reis and Källén (2010), Jimenez-Solem *et al.* (2012)
Sertraline	VSD	1008	9	89.29	26.35	<0.001	36.67	0.01	Wichman *et al.* (2009), Jimenez-Solem *et al.* (2012)
Valproic acid[b]	Polydactyly	1226	6	48.94	7.23	<0.001	15.53	0.009	Wyszynski *et al.* (2005), Diav-Citrin *et al.* (2008a), Tomson *et al.* (2011)

ASD, atrial septal defect; SSRI, selective serotonin-reuptake inhibitor; VSD, ventricular septal defect.
[a]All data originate from population-based cohort studies, unless mentioned otherwise. Prevalence (prev) per 10 000 live births.
[b]Data from register-based cohort studies.

validity of the data obtained on medication use and the diagnosis of birth defects. Medical records and registries may overestimate medication use during pregnancy due to non-compliance (Olesen *et al.*, 2001), whereas self-reported methods may underestimate drug exposure (van Gelder *et al.*, 2013b). For data on the diagnosis of birth defects, medical records are regarded as the gold standard. In large studies, however, obtaining medical records may not be feasible, but data obtained from linkage with medical birth registries or through maternal report lead to underascertainment (Rasmussen *et al.*, 1990; Amini *et al.*, 2009) and often lack clinical details, which does not allow compilation of homogeneous case groups.

When considering the results from this literature review in light of recent studies determining which medications are most commonly used by pregnant women (Mitchell *et al.*, 2011; Thorpe *et al.*, 2013; van Gelder *et al.*, 2013a), it is a cause of concern that the drugs most often dispensed in the first trimester of pregnancy are not necessarily the drugs for which potential teratogenic risks have been studied. For example, studies on inducers of oxidative stress were sparse and often had small sample sizes, while this is the drug group for which high first trimester prescription rates have been observed (van Gelder *et al.*, 2013a). More specifically, for a number of commonly used specific prescription medications (Mitchell *et al.*, 2011; Thorpe *et al.*, 2013), including salbutamol and salmeterol, both vasoactive drugs, ondansetron and escitalopram, which may influence serotonin signalling, and follitropin, an endocrine disrupting drug, data on the teratogenic risks are very limited. In contrast, many of the studies included determined the teratogenic potential of antiepileptic drugs, for which prescription rates are very low. Reassuringly, the trend of increasing prescription rates for SSRIs (Alwan *et al.*, 2011; van Gelder *et al.*, 2013a) seems to be accompanied by increasing numbers of studies on the teratogenic risks of SSRIs. From a public health perspective, future research should focus on those drugs that are most commonly used during pregnancy and for which the teratogenic risks are as yet unknown, such as the specific medications listed above, iron preparations, serotonin receptor agonists or antagonists, drugs used in fertility treatment and dihydrofolate reductase inhibitors. A research focus on commonly used drugs in combination with

Table V Associations between selected medications and specific birth defects observed in case–control studies that were confirmed in at least one other study.

Drug	Birth defect	Confirmed in	Refuted in	References
Acetaminophen	Cleft palate	CC-P PBC ($n = 26\,479$)	CC-P (2x)	Thulstrup *et al.* (1999), Källén (2003), Puhó *et al.* (2007), Rebordosa *et al.* (2008), Feldkamp *et al.* (2010)
Antihypertensive	ASD	CC-P PBC ($n = 1430$) PBC (ACEi; $n = 268$)	–	Cooper *et al.* (2006), Caton *et al.* (2009), Lennestål *et al.* (2009), Karthikeyan *et al.* (2011)
Antihypertensive	Coarctation of aorta	CC-P PBC ($n = 1430$)	–	Caton *et al.* (2009), Lennestål *et al.* (2009)
Antihypertensive	Pulmonary valve stenosis	CC-P PBC (ACEi, $n = 268$)	PBC ($n = 1430$)	Cooper *et al.* (2006), Caton *et al.* (2009), Lennestål *et al.* (2009), Karthikeyan *et al.* (2011)
Clomiphene	Anencephaly	CC-M CC-P	CC-P PBC ($n = 1711$)	Hack *et al.* (1972), Ahlgren *et al.* (1976), Gorlitsky *et al.* (1978), Correy *et al.* (1982), Kurachi *et al.* (1983), Reefhuis *et al.* (1999), Whiteman *et al.* (2000), Tulandi *et al.* (2006), Reefhuis *et al.* (2011)
Clomiphene	Coarctation of aorta	CC-P (2*x*)	PBC ($n = 1711$)	Hack *et al.* (1972), Ahlgren *et al.* (1976), Gorlitsky *et al.* (1978), Correy *et al.* (1982), Kurachi *et al.* (1983), Tulandi *et al.* (2006), Reefhuis *et al.* (2011), Wollins *et al.* (2011)
Fluoxetine	Craniosynostosis	CC-P RBC ($n = 643$)	CC-P PBC ($n = 1519$)	Pastuszak *et al.* (1993), Chambers *et al.* (1996), McElhatton *et al* (1996), Alwan *et al.* (2007), Louik *et al.* (2007), Diav-Citrin *et al.* (2008b), Einarson *et al.* (2009), Reis and Källén (2010)
Naproxen	Cleft lip ± cleft palate	CC-P (2*x*)	–	Källén (2003), Hernandez *et al.* (2012)
NSAIDs	VSD	CC-P PBC ($n = 5560$)[b]	CC-P PBC ($n = 5560$)[c]	Ericson and Källén (2001), Bateman *et al.* (2004), Cleves *et al.* (2004), van Gelder *et al.* (2011)
Oxprenolol	Cleft lip ± cleft palate	CC-M[a] CC-P	–	Puhó *et al.* (2007)
Phenytoin	Cleft lip ± cleft palate	CC-M[a] CC-P	–	Puhó *et al.* (2007)
Progestin/ progesterone	Hypospadias	CC-P PBC ($n = 2683$)	–	Dillon (1970), Harlap *et al.* (1975), Mau (1981), Katz *et al.* (1985), Resseguie *et al.* (1985), Rock *et al.* (1985), Yovich *et al.* (1988), Carmichael *et al.* (2005), Colvin *et al.* (2010)
SSRIs	Craniosynostosis	CC-P PBC ($n = 6555$)[b]	CC-P PBC ($n = 6555$)[c]	Alwan *et al.* (2007), Källén and Otterblad Olausson (2007), Louik *et al.* (2007)
Valproic acid	ASD	CC-M PBC ($n = 224$) RBC ($n = 325$)	–	Jäger-Roman *et al.* (1986), Bertollini *et al.* (1987), Kaneko *et al.* (1988), Thisted and Ebbesen (1993), Canger *et al.* (1999), Holmes *et al.* (2001), Wyszynski *et al.* (2005), Meador *et al.* (2006), Vajda *et al.* (2006), Diav-Citrin *et al.* (2008a), Juárez-Olguín *et al.* (2008), Jentink *et al.* (2010a), Mawer *et al.* (2010)
Valproic acid	Cleft palate	CC-M RBC ($n = 325$)	–	Wyszynski *et al.* (2005), Vajda *et al.* (2006), Diav-Citrin *et al.* (2008a), Jentink *et al.* (2010a)
Valproic acid	Craniosynostosis	CC-M PBC ($n = 492$) RBC ($n = 325$)	–	Jäger-Roman *et al.* (1986), Bertollini *et al.* (1987), Kaneko *et al.* (1988), Thisted and Ebbesen (1993), Canger *et al.* (1999), Holmes *et al.* (2001), Wide *et al.* (2004), Wyszynski *et al.* (2005), Meador *et al.* (2006), Vajda *et al.* (2006), Diav-Citrin *et al.* (2008a), Juárez-Olguín *et al.* (2008), Jentink *et al.* (2010a), Mawer *et al.* (2010)
Valproic acid	Hypospadias	CC-M PBC ($n = 248$) RBC ($n = 625$)	CC-P	Jäger-Roman *et al.* (1986), Bertollini *et al.* (1987), Kaneko *et al.* (1988), Thisted and Ebbesen (1993), Canger *et al.* (1999), Holmes *et al.* (2001), Wide *et al.* (2004), Wyszynski *et al.* (2005), Meador *et al.* (2006), Vajda *et al.* (2006), Diav-Citrin *et al.* (2008a), Juárez-Olguín *et al.* (2008), Jentink *et al.* (2010a), Mawer *et al.* (2010)

Continued

Table V *Continued*

Drug	Birth defect	Confirmed in	Refuted in	References
Valproic acid	Spina bifida	CC-M (2*x*) PBC ($n = 224$) RBC ($n = 444$)	–	Jäger-Roman *et al.* (1986), Lindhout and Schmidt (1986), Bertollini *et al.*, (1987), Kaneko *et al.* (1988), Thisted and Ebbesen (1993), Canger *et al.* (1999), Reefhuis *et al.* (1999), Holmes *et al.* (2001), Wyszynski *et al.* (2005), Meador *et al.* (2006), Vajda *et al.* (2006), Diav-Citrin *et al.* (2008a), Juárez-Olguín *et al.* (2008), Jentink *et al.* (2010a), Mawer *et al.* (2010)

ACEi, angiotensin-converting enzyme inhibitors; ASD, atrial septal defect; CC-M, case–control study with malformed controls; CC-P, case–control study with population controls; NSAID, non-steroidal anti-inflammatory drug; PBC, population-based cohort; RBC, register-based cohort; SSRI, selective serotonin-reuptake inhibitor; VSD, ventricular septal defect.
[a]Used the same cases as the corresponding CC-P.
[b]European reference population.
[c]US reference population.

drugs for which the largest effects may be expected based on their mechanism of action would provide the best opportunities to improve health and well-being of future generations.

Conclusions

Our study confirms the lack of knowledge on the teratogenic effects of medical drugs that was reported previously (Adam *et al.*, 2011; Thorpe *et al.*, 2013). The study design characteristics of the studies included may raise some concern due to the absence of reference groups for almost half of the cohort studies, not reporting participation or follow-up rates, and use of data collection methods with questionable validity. In addition, current knowledge on the teratogenic risks of medical drugs is not associated with prescription rates: many uncertainties exist regarding the fetal safety of drugs that are frequently dispensed, while the adverse effects of drugs that are less often used but are already known to increase the risks of specific birth defects are still being studied. These studies may yield important information from a mechanism-based point of view, but from a public health perspective it is more important to study prevalent exposures to potentially benefit the largest number of people in future generations by primary prevention. Therefore, large-scale, well-designed epidemiologic studies are needed in order to enable prescribers to make evidence-based decisions on whether or not the beneficial effects of treatment outweigh the possible risks for the developing fetus.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' roles

Study concept and design: all authors. Acquisition of the data: MMHJvG. Analysis of the data: MMHJvG. Interpretation of the data: all authors. Wrote the first draft of the manuscript: MMHJvG. Critical revision of the manuscript for important intellectual content: all authors.

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Conflict of interest

None declared.

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