

OBSTETRICS

The fetal safety of cetirizine: An observational cohort study and meta-analysis

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Cetirizine, a second-generation antihistamine, is an active metabolite of hydroxyzine used in the treatment of allergies, but the data on fetal safety are inconclusive. Pregnant women who were counselled by the 'Motherisk Program' regarding cetirizine exposure were enrolled in a cohort study and compared with pregnant women counselled for non-teratogenic exposures. The objective was to measure the rate of adverse pregnancy outcomes. Subsequently, we also conducted a meta-analysis of cohort studies that examined the pregnancy outcomes of women exposed to hydroxyzine or cetirizine during pregnancy. In the cohort study, there were no significant differences in the rates of major malformations between the cetirizine exposed and comparison group. In the meta-analysis, cetirizine was not associated with increased teratogenic risk. In contrast, a meta-analysis of cetirizine and hydroxyzine studies showed a marginal association with major malformations. Cetirizine is not associated with a clinically important increase in risk of adverse fetal outcomes.

Keywords: Cetirizine, cohort study, hydroxyzine, meta-analysis, pregnancy outcome

Background

Second-generation antihistamines (astemizole, loratadine, cetirizine and fexofenadine) provide symptomatic relief of allergic disorders without the adverse effects of first-generation antihistamines, mostly CNS and anticholinergic effects. Second-generation antihistamines are preferred particularly by patients with a higher risk for development of adverse effects, including sedation and impaired sleep architecture (Casale et al. 2003; Morgan et al. 2005).

Cetirizine hydrochloride (Reactine)[®], a non-prescription selective, second-generation histamine (H₁) receptor antagonist, is a major active metabolite of hydroxyzine (first-generation antihistamines) with anti-allergic, anti-histaminic and anti-inflammatory effects. Cetirizine is the most potent antihistamine available and is more effective than loratadine and other H₁ receptor antagonists in inhibiting histamine-induced wheal responses (swelling) and flare responses (vasodilation) (Golightly and Greos 2005). Due to its high potency, cetirizine may be appropriate for most severe allergy symptoms that are unresponsive to other antihistamines. It has a rapid onset, a long duration of activity and

low potential for interaction with drugs that are metabolised by the hepatic cytochrome P450 system (Golightly and Greos 2005; Curran et al. 2004).

It is estimated that up to 20–30% of women of childbearing age, experience allergic rhinitis and 4–7% suffer from asthma during pregnancy, making them two of the most common groups of medical conditions that complicate pregnancy. The symptoms may vary from mild sneezing, itching, which commonly can be relieved by avoiding the source of allergy, to severe nasal obstruction that may require pharmacotherapy (Keles 2004). Product labels state that medications for allergic rhinitis should be avoided during pregnancy due to lack of fetal safety data (Mazzotta et al. 1999) and because half of all pregnancies are unplanned (Finer and Zolna 2011) and this may lead to fetal exposure to antihistamine before a woman knows she is pregnant.

No teratogenic effects were detected with oral cetirizine doses of 60, 188 and 133 times the maximum clinically studied human dose in mice, rats and rabbits, respectively (Kamijima et al. 1994). However, the animal studies are not necessarily indicative of adverse effects during pregnancy at clinically relevant doses and are not always predictive of human responses. There are limited human studies reporting cetirizine exposure in pregnancy and pregnancy outcomes. A small prospective, comparative study conducted by Motherisk following 39 mothers exposed to cetirizine (37 in the first trimester) did not find any differences in pregnancy outcomes between the exposed and comparison groups (Einarson et al. 1997). The most recent data were from the Berlin teratogen information service, with 196 women exposed in any trimester (11% in the first trimester), and did not show increased risk of birth defects or other adverse outcomes (Weber-Schoendorfer and Schaefer 2008). A recent review from the Food and Drug Administration, with the American College of Allergy, Asthma, Immunology and American College of Obstetrics and Gynecology, stated that cetirizine should be considered mainly for the second and third semester of pregnancy as a second-generation agent for allergic conditions in pregnancy if first-generation antihistamine agents are not tolerated (Blais 2003). These statements suggest to patients and healthcare providers that the fetal safety of cetirizine is still questioned. Because half of all pregnancies are unplanned, this type of message may increase anxiety among many exposed women.

Hence, our study objectives were as follows: the primary objective was to determine whether cetirizine hydrochloride

exposure during the first trimester of human pregnancy is associated with an increased rate of major birth defects above the baseline rate of 1–3% in the general population. The secondary objective was to determine the rates of spontaneous abortions, stillbirths, birth weight and neonatal complications following cetirizine hydrochloride exposure.

Methods

This study includes an observational cohort study and a meta-analysis of all available studies to date.

Observational cohort study

Study design

This was a prospectively collected observational cohort study.

Settings

This study was conducted at the Motherisk Program located at the Hospital for Sick Children in Toronto. The Motherisk Program is a counselling service that provides pregnant, breast-feeding women, and health professionals information on the safety and risks of exposures to prescription and over-the-counter medications, natural health products, chemicals, radiation, and infectious diseases (Koren et al. 1986). Women who called the Motherisk Program between 1 January 2004 and 31 December 2007, were enrolled.

Study participants

Three groups of women were recruited. The first group included pregnant women exposed to cetirizine hydrochloride during the first trimester of pregnancy. The second group included women who called the general Motherisk line about exposure to non-teratogenic agents (control group). The control group was matched to the study group (first group) according to maternal age at the time of conception (± 2 years) and gestational age at the time of first call to Motherisk (± 2 weeks). The third group included pregnant women exposed to cetirizine hydrochloride during the second and/or third trimesters of pregnancy (disease matched non-first trimester exposure).

Inclusion criteria

1. Women who contacted Motherisk regarding information on the safety or risk of using cetirizine hydrochloride for the treatment of seasonal allergic rhinitis, chronic idiopathic urticarial and any other allergy at any stage of pregnancy
2. Women who contacted Motherisk regarding information on the safety of vitamins or other non-teratogenic exposures (i.e. acetaminophen, etc.) at any stage of their pregnancy.

Exclusion criteria

1. Women who were exposed to teratogenic agents (e.g. anticonvulsants, isotretinoin, warfarin)
2. Women with medical conditions that may be associated with birth defects or any pregnancy complications (e.g. diabetes, alcohol abuse).

Data collections

All women in the study group were recruited when they first contacted the Motherisk program, regarding the safety of cetirizine hydrochloride during pregnancy. At the time of their first call, the study protocol was explained and oral informed consent was obtained. At this initial call, we collected demographic data,

general health information and information on exposure to any drugs used concomitantly with a special focus on the details about cetirizine exposure (dose, duration and adverse effects) on a previously developed structural questionnaire. The women were re-interviewed 6 months or more after delivery to obtain outcome data using standardised follow-up forms. In addition, the mothers' pre-pregnancy weight and weight at the time of delivery were recorded. Subsequent to the completion of the pregnancy follow-up and in order to confirm medical details of the babies' health, it was necessary to obtain the verbal permission of the women to send a letter to their children's healthcare providers. The letters were sent to the caller's physicians (family physicians or paediatricians) for verification of the information obtained from the mothers. The doctors were asked to complete questionnaires and the state of general health of the babies, as well as major and minor malformations. The follow-up procedures have been approved by the Sick Children Hospital's Research Ethics Committee.

Statistical analysis

Outcome end-points of interest were compared among those exposed to cetirizine in the first trimester group and control groups (not exposed to cetirizine and non-first trimester exposed to cetirizine) with the Student's *t*-test with Bonferroni correction, χ^2 or the Fisher's exact test whenever suitable.

Meta-analysis

A systematic review and meta-analyses were conducted on all observational cohort studies published (including the current cohort study) that address the effect of cetirizine on pregnancy outcomes and cohort studies that had hydroxyzine as an exposed group. Cetirizine is an active carboxylic acid metabolite of hydroxyzine (first generation antihistamine) (Barnes et al. 1993). Combining the extracted cetirizine studies and hydroxyzine studies in one meta-analysis is therefore biologically plausible and will increase the sample size to estimate the fetal safety of cetirizine and hydroxyzine during pregnancy.

Search strategy

A systematic review was performed to retrieve all published articles involving cetirizine or hydroxyzine exposure during pregnancy. This review followed the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup et al. 2000). Searches were conducted using electronic databases for possibly relevant articles that were published in any language up to December 2012. Included databases were PubMed, SCOPUS, EMBASE and TOXLINE. The literature was searched using drug names '(Cetirizine, Cetirizine Dihydrochloride, Zyrtec, Reactine, Zirtek, Voltric, Cetirizine AL, Hydroxyzine, Vistaril, Durrax or Atarax)' and drug categories based on pharmacological action '(Histamine H1 Antagonists, H1 Antihistaminic, H1 Receptor Blockers, Non-Sedating Histamine H1 Antagonists, Second Generation H1 Antagonists or first Generation H1 Antagonists)'.

Subsequently, these terms were combined with various MeSH categories (including pregnancy, pregnancy complications, abnormalities, embryonic and fetal development, maternal exposure, teratogens) and keywords (including birth defect, abnormality, malformation, embryopathy). The reference lists of all retrieved studies, including reviews, were examined for articles not identified by the search strategy.

Study selection

Studies were included in the meta-analysis if they met the following criteria:

1. Observational cohort studies, but not case-control or case reports
2. Studies that reported the incidence of malformation and/or other pregnancy outcomes in the offspring of women who were or were not exposed to cetirizine during pregnancy (use of a control or comparison group)
3. Sufficient data to calculate the odds ratios
4. Reported data that was not included in a later report by the same group of investigators (to prevent duplication of overlapping reports)
5. A sample size larger than ten
6. Human studies only.

Two authors reviewed the studies to determine whether or not they met the inclusion criteria.

Data extraction and analysis

A data extraction form was used to collect the information from each study. This information included: first author, year of publication, study design, study location, years of study and outcome measures. Outcome measures were extracted for either the cetirizine or hydroxyzine exposed group and the control group and these measures included the whole group number, live birth number, malformed cases, spontaneous and therapeutic abortion cases and prematurity (< 37 weeks' gestation) cases. All the data was arranged in 2×2 tables to calculate the odd ratios. A random-effects meta-analysis model was used to combine the risk data for malformation and other pregnancy outcomes by using a statistical program called Comprehensive Meta Analysis Version 2.0. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Heterogeneity of effects was assessed using the Q statistic. Three meta-analyses were conducted to assess the risk of major malformations, one for cetirizine studies, one for hydroxyzine studies and another one for combined hydroxyzine and cetirizine studies. Two meta-analyses were performed for the other pregnancy outcomes (spontaneous abortion and prematurity).

Results

Cetirizine cohort study

The cohort study included 78 pregnancies exposed to cetirizine during the first trimester (with or without second or third exposure); 56 pregnancies exposed to cetirizine during second and/or third trimester (no first trimester exposure); and 134 pregnancies exposed to non-teratogenic drugs. Mean of maternal age of the three groups were similar (between 32 and 33 years).

Table I. Outcomes of pregnancies in fetus that had 1st trimester cetirizine exposure and control group.

Outcome	Cetirizine T1 group	Control group	<i>p</i> value
Live birth	73/81	128/135	0.27
Spontaneous abortion	5/81	7/135	0.77
Therapeutic abortion	1/81	0/135	0.38
Stillbirth	2/81	0/135	0.14
Major malformations*	2/76	3/129†	1.00
Minor malformations*	2/76	1/128	0.61
Birth weight (g)‡	3,317 ± 704	3,547 ± 532	<0.01
Gestational age (weeks)‡	39 ± 2.56	40 ± 1.59	<0.006
Prematurity‡	11/73	3/128	<0.001
Caesarean section‡	24/70	22/94	0.16
Neonatal distress‡	9/73	9/128	0.21

*Of live births, therapeutic abortion and stillbirth. †Of live births, therapeutic abortion, stillbirth and one case of spontaneous abortion. ‡Of live births.

Table II. Outcomes of pregnancies in fetuses that had first trimester cetirizine exposure and in fetuses exposed to cetirizine during second and/or third trimester.

Outcome	Cetirizine (T1) group	Cetirizine (non-T1) group	<i>p</i> value
Live birth	73/81	57/57	0.02
Spontaneous abortion	5/81	0/57	0.08
Therapeutic abortion	1/81	0/57	1.00
Stillbirth	2/81	0/57	0.51
Major malformations*	2/76	0/57	0.51
Minor malformations*	2/76	1/57	1.00
Birth weight (g)†	3,317 ± 704	3,462 ± 558	0.21
Gestational age (weeks)†	39 ± 3	39 ± 2	0.27
Prematurity†	11/73	4/57	0.18
Caesarean section†	24/70	16/56	0.57
Neonatal distress†	9/73	11/57	0.33

*Of live births, therapeutic abortion and stillbirth. †Of live births.

In the group exposed to cetirizine during the first trimester, there were a total of 73 live births, counting three sets of twins, five spontaneous abortions, one therapeutic abortion, two fetal deaths and eleven premature births. Two cases with major malformations were reported in the cetirizine first trimester exposed group: the first case was a child born with a hip dysplasia and the other case was Down's syndrome, detected at 14 weeks and ending in therapeutic abortion at 18–19 weeks. Two cases with minor malformations were reported in the same group: periventricular leukomalacia was diagnosed in the same child that was born with a hip dysplasia, and the second case was a child born with a tongue tie.

In the group exposed to cetirizine during only the second and/or third trimesters, there were 57 live births including one set of twins and four premature cases. There were no major malformations and one minor malformation. The child with the minor malformation was born with oesophageal sphincter, which was not fully formed until 4–5 months. This defect runs in the paternal family.

In our control group, there were 128 live births, including one set of twins, seven spontaneous abortions and three premature cases. In this control group, there were three major malformations and one minor malformation. One of the major malformations was Trisomy 13 found in one of the spontaneously aborted fetuses. The other two major malformations were infants born with undescended testes associated with exstrophy of the bladder and right inguinal hernia. The minor malformation case was an infant born with an umbilical hernia.

Two comparisons were made, one between the group exposed to cetirizine during the first trimester and the control group (Table I) and the other between the group exposed to cetirizine during the first trimester and the exposed group to cetirizine during the second or third trimesters (Table II). There was no difference in the rates of major or minor malformation, live births, spontaneous or therapeutic abortions, still births, and rates of caesarean or neonatal distress among the groups. However, there were significant differences between the exposed group to cetirizine during the first trimester and the control group in rates of prematurity ($p = 0.001$), birth weight ($p = 0.01$) and gestational age at birth ($p = 0.006$). These differences were not detected between the group exposed to cetirizine in the first trimester and the group exposed to cetirizine during the second or third trimesters. Moreover, subanalysis revealed that offspring of women with asthma, twins and smoking cases receiving cetirizine exhibited significantly lower birth weights and rates of prematurity. After excluding them from the study group, these differences from the control group disappeared (Table III).

Table III. Outcomes of pregnancies in fetuses that had first trimester cetirizine exposure and control group after removing of asthma, twins and smoking cases.

Outcome	Cetirizine T1 group	Control group	<i>p</i> value
Live birth	56/64	119/126	0.15
Birth weight (g)*	3,449 ± 695	3,560 ± 512	0.24
Gestational age (weeks)*	39 ± 3	40 ± 1	0.11
Prematurity*	5/56	3/119	0.11

*Of live births.

Meta-analytic results

The electronic search identified 1,500 literature titles. After removing all duplicates and reviewing titles and/or abstracts to exclude the animal studies, non-cohort studies, review articles without original data and articles that addressed pregnancy outcomes of antihistamines exposure other than cetirizine or hydroxyzine, twelve articles were reviewed in detail. Ten studies fulfilled the inclusion criteria for the meta-analysis, including the current cohort study. The other four were excluded because: one of them had no healthy control groups (Wilton et al. 1998); one was a case-control study (Gilboa et al. 2009); one study focussed only on one type of malformation (Carter et al. 1980); and one study was published as an abstract (Einarson et al. 1993) and the same data was included in a peer-reviewed publication (Einarson et al. 1997) (Figure 1).

Of the ten studies included in our meta-analyses, four studies included women on hydroxyzine (Erez et al. 1971; Briggs

et al. 1994; Heinonen et al. 1977; Diav-Citrin et al. 2003); four studies were on cetirizine (including the current study) (Weber-Schoendorfer and Schaefer 2008; Kallen 2002; Paulus et al. 2004) and two studies were on hydroxyzine and cetirizine (Einarson et al. 1997; Schatz and Petitti 1997) (Table IV). All the included studies measured the risk of major malformations, whereas five studies assessed the risk of spontaneous abortion (Einarson et al. 1997; Weber-Schoendorfer and Schaefer 2008; Erez et al. 1971; Paulus et al. 2004; current study), and two studies also assessed prematurity (Weber-Schoendorfer and Schaefer 2008; current study). The Q-statistic for heterogeneity of effects was not significant for any of the analyses ($p > 0.05$).

Meta-analysis of hydroxyzine studies that assessed the risk of major malformations

Data from six studies with a total of 1,082 women exposed to hydroxyzine and 279,480 unexposed controls were included in the meta-analysis. The risk for congenital malformations in the offspring of women exposed to hydroxyzine was not higher than those in the controls that were not exposed to hydroxyzine (OR 1.21; 95% CI 0.92–1.59) (Figure 2).

Meta-analysis of cetirizine studies that assessed the risk of major malformations

Six potentially relevant cetirizine studies fulfilled the inclusion criteria for the meta-analysis, two of which were excluded because they reported two zero events in the exposed and in the control groups (ORs could not be calculated from these studies) (Einarson et al. 1997; Schatz and Petitti 1997). A total of 1,293

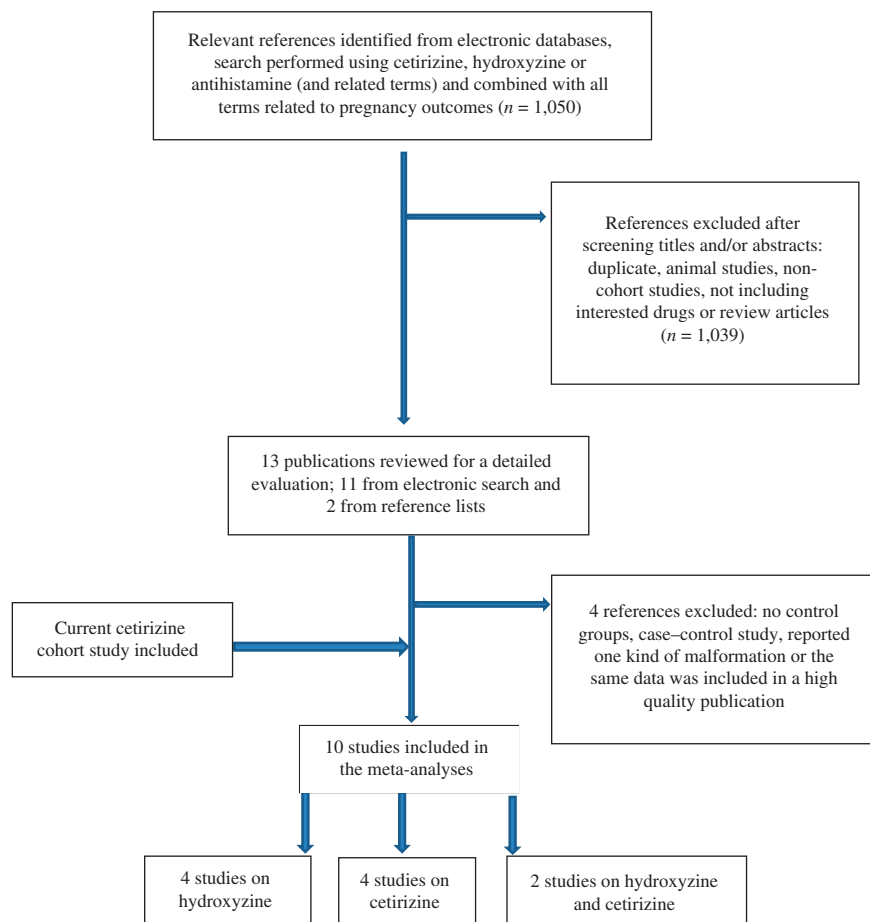


Figure 1. Diagram for search strategy and study selection for the meta-analyses.

Table IV. Characteristics of the nine studies included in the meta-analyses.

Study	Type of medication exposures	No. of exposed women	No. of controls	Pregnancy outcome evaluated	Location of the study	Publication type
Erez et al. (1971)	Hydroxyzine	79	36	Malformed, SA	Turkey	Peer review journal
Heinonen et al. (1977)	Hydroxyzine	50	50,232	Malformed	USA	Book
Briggs et al. (1994)	Hydroxyzine	828	228,273	Malformed	USA	Book (PC), control group published by Schatz and Petitti (1997)
Schatz and Petitti (1997)	Hydroxyzine, cetirizine	76	82	Malformed	USA	Guest editorial
Einarson et al. (1997)	Hydroxyzine, cetirizine	92	92	Malformed, SA	Canada	Peer review journal
Kallen et al. (2002)	cetirizine	917	402,628	Malformed	Sweden	Peer review journal
Diav-Citrin et al. (2003)	Hydroxyzine	33	844	Malformed	Israel	Peer review journal
Paulus et al. (2004)	cetirizine	123	470	Malformed, SA	Germany	Abstract
Weber and Schaefer (2008)	cetirizine	177	1,521	Malformed, SA, P	Germany	Peer-review journal
Current study	cetirizine	76	129	Malformed, SA, P	Canada	Peer-review journal

PC, personal communication; SA, spontaneous abortion; P, prematurity.

exposed and 404,748 unexposed controls from the remaining four studies were included in the meta-analysis. The OR (95% CI) for incidence of abnormalities after exposure to cetirizine was 1.26 (0.93–1.69) (Figure 3).

Meta-analysis of combined hydroxyzine and cetirizine studies that assessed the risk of major malformations

This meta-analysis combined all hydroxyzine and cetirizine studies, with a total of 2,448 exposed and 684,305 unexposed controls. The OR (95% CI) for incidence of abnormalities after exposure to hydroxyzine or cetirizine was 1.23 (1.01–1.51), which was marginally significant (Figure 4).

Meta-analysis of hydroxyzine and cetirizine studies that assessed the risk of spontaneous abortion

Five studies examined the risk of spontaneous abortion for pregnant women exposed to hydroxyzine or cetirizine, and were included in the meta-analysis (598 exposed and 2,491 unexposed controls). The OR (95% CI) for the incidence of spontaneous abortion after exposure to hydroxyzine or cetirizine was 1.09 (0.77–1.53) (Figure 5).

Meta-analysis of cetirizine studies that assessed the risk of prematurity

Only two studies reported prematurity in the cetirizine-exposed and control groups, including the current cohort study; there were no hydroxyzine studies that examined the risk of prematurity

(total of 233 exposed and 1,640 unexposed controls). The OR (95% CI) for incidence of prematurity after exposure to cetirizine was 1.47 (0.31–7.01) (Figure 6).

Discussion

Cohort study

The results of our controlled cohort study suggest that this antihistamine, when taken during organogenesis, is not associated with an increased risk of major malformations or spontaneous abortions when compared with non-teratogenic medications taken by healthy pregnant women. Importantly, this association was also not present when compared with disease-matched women who took cetirizine after the organogenesis period. These results agree with several other human studies; that there is no risk above the baseline for major malformations when cetirizine is taken during pregnancy (Einarson et al. 1997; Weber-Schoendorfer and Schaefer 2008).

There were statistically significant differences between the first trimester (T1) exposed group and the control group in the rate of twins ($p = 0.03$) and maternal asthma ($p = 0.0007$). These two confounders are strongly associated with prematurity (Murphy et al. 2011; Refuerzo 2012). The control group was not matched for smoking, and smoking is also a known cause of prematurity (Shah and Bracken 2000). We analysed the data after removing these confounders and examined whether the association between cetirizine exposure during organogenesis and prematurity is still evident. After removing all twins, asthma and smoking cases from both groups, the association between

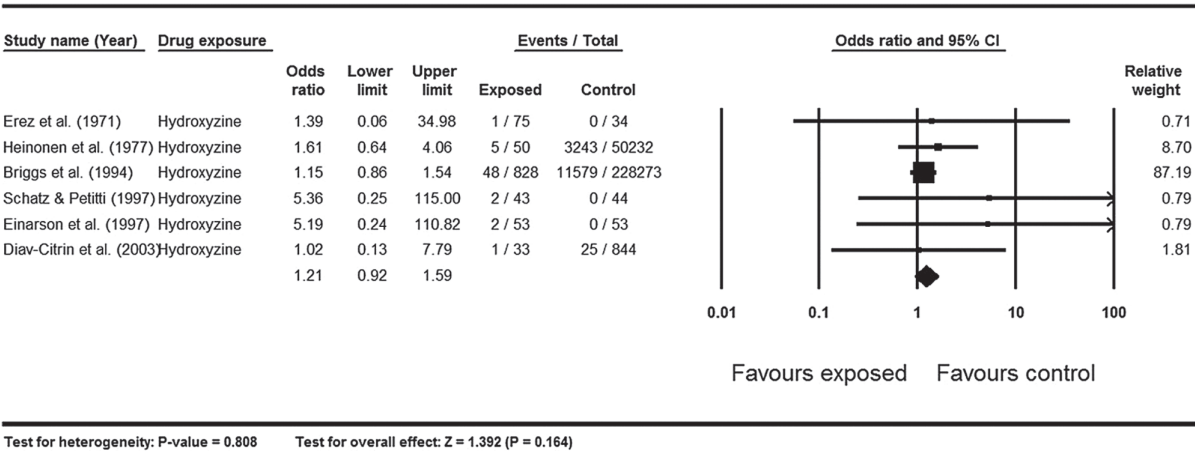


Figure 2. Odd ratios (ORs) and 95% confidence intervals (CIs) for malformations in offspring of women using hydroxyzine during pregnancy vs control groups.

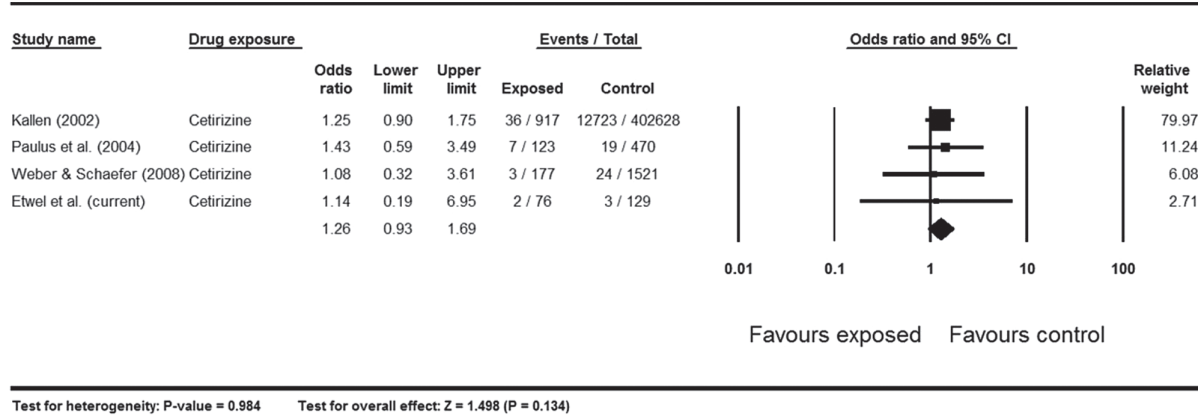


Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for malformations in offspring of women using cetirizine during pregnancy vs control groups.

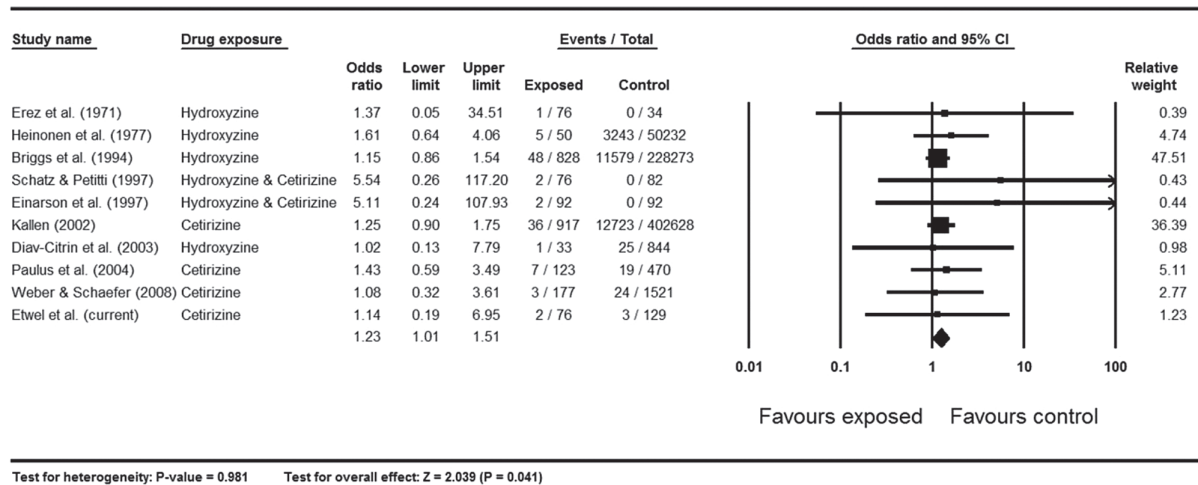


Figure 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for malformations in offspring of women using hydroxyzine or cetirizine during pregnancy vs control groups.

cetirizine and prematurity ($p = 0.11$), birth weight ($p = 0.24$) and gestational age at birth ($p = 0.11$), disappeared (Table III). Just as important, the association between prematurity and cetirizine use during the first trimester is not present when we compared it with a disease-match group. These data highlight the importance of controlling for confounding by indication in pregnancy outcome studies.

Our cohort study has limited power to show increased teratogenic risk. Approximately 200 cases and an equal number of matched comparisons are needed to detect (with a power of 80% and $\alpha = 0.05$) a five-fold increased teratogenic risk above the baseline of 3%. To overcome this hurdle, we increased the sample size by combining the previous human studies in one meta-analysis and estimated the major malformations and other pregnancy outcomes.

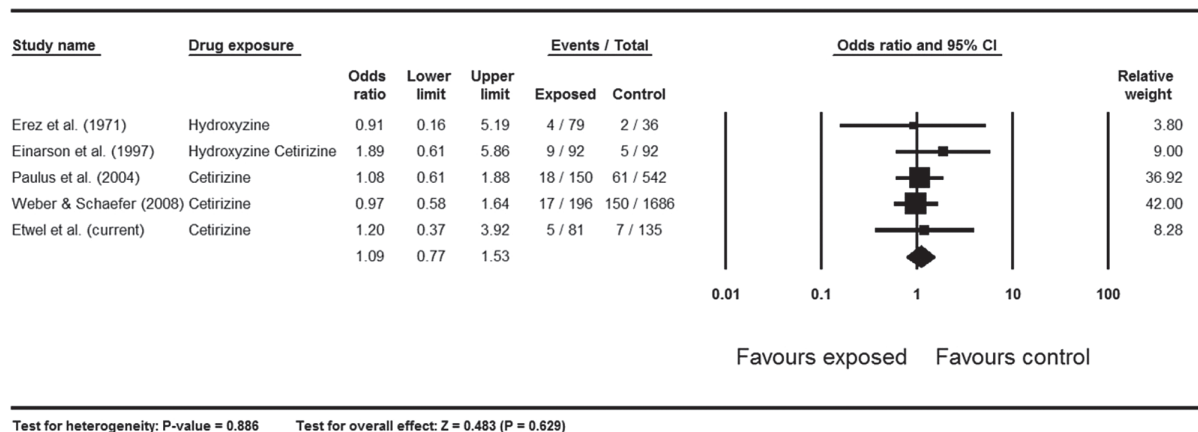


Figure 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for spontaneous abortion for women using hydroxyzine or cetirizine during pregnancy vs control groups.

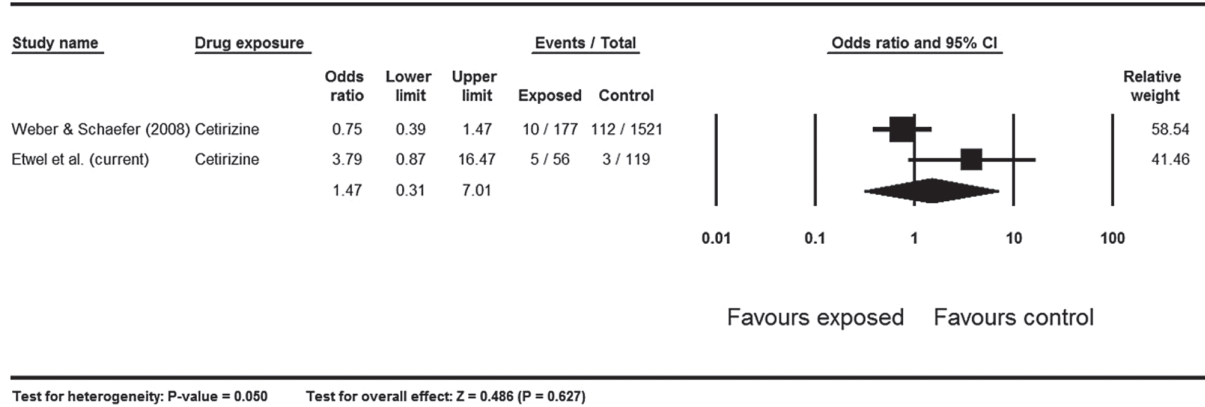


Figure 6. Odd ratios (ORs) and 95% confidence intervals (CIs) for prematurity in offspring of women using cetirizine during pregnancy vs control groups.

Meta-analyses

The meta-analyses suggest that the use of hydroxyzine or cetirizine does not appear to be associated with a major increased risk for malformations. Although the meta-analysis combining hydroxyzine and cetirizine studies shows a marginal association of an increased risk for major malformation (OR 1.31; 95% CI 1.01–1.51), this result may not be clinically significant. In particular, as shown in our cohort study, there may be confounding indications, as several studies suggested an increased risk of malformation in offspring of asthmatic patients.

These results were compatible with a case–control study published in 2009 (Gilboa et al. 2009) that looked at the association between birth defects and antihistamine use during early pregnancy. Moreover, a non-interventional observational cohort study published in 1998 (Wilton et al. 1998) followed women who were exposed to newly marketed drugs at that time, one of them being cetirizine. The results showed that the proportion of live infants with a congenital abnormality born to mothers exposed to newly marketed drugs in the first trimester were similar to the percentage of congenital anomalies in the general population (no congenital cases reported after cetirizine exposure).

Furthermore, secondary analyses of other pregnancy outcomes showed no apparent increased risk for spontaneous abortions or prematurity or after exposure to cetirizine or hydroxyzine.

In conclusion, based on the current cohort study and meta-analysis, cetirizine is not associated with an increased risk of major malformations or other adverse fetal outcomes. The study highlights the importance of control for confounding by indication, in this case asthma, which may adversely affect pregnancy outcomes irrespective of cetirizine use.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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