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Risk of Hypospadias in Offspring of Women Using Loratadine during Pregnancy

A Systematic Review and Meta-Analysis

Eleanor B. Schwarz,[1] *Myla E. Moretti*,[2] *Smita Nayak*[1] and *Gideon Koren*[2]

1 Division of General Internal Medicine, Department of Medicine, Center for Research on Health Care, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
2 Motherisk Program, Division of Clinical Pharmacology/Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada

Abstract

Background: Loratadine, a second-generation antihistamine, is commonly used to treat seasonal allergies. Some studies have suggested that use of loratadine by pregnant women increases the risk of hypospadias in male offspring.

Objective: This meta-analysis was designed to assess the strength of the association between loratadine and hypospadias.

Methods: To locate pertinent articles published in any language from January 1989 until August 2007, we searched electronic databases (MEDLINE, OVID, EMBASE, SCOPUS, TOXLINE Special, ReproTox, TERIS, CINAHL and others), conference proceedings and bibliographies. Studies were eligible for this analysis if they were cohort, case-control or case series studies that reported the incidence of hypospadias in the offspring of women who were or were not exposed to loratadine during pregnancy. Two authors independently extracted information on study design, participant characteristics, measures of outcome, control for potential confounding factors and risk estimates using a standardized data collection form. The Newcastle-Ottawa Scale was then used to assess the quality of each study. We used a random-effects meta-analysis model to combine the risk data.

Results: In 1402 potentially relevant titles, we found three case-control studies and seven cohort studies that reported the incidence of hypospadias or other congenital malformations in offspring of women who did or did not use loratadine during pregnancy. Together the studies in our meta-analysis provided information about 453 053 male births in Brazil, Canada, Denmark, Israel, Italy, Sweden, the UK and the US.

Of 2694 male infants born to women using loratadine, 39 (1.4%) had hypospadias. Of 450 413 male infants born to women not using loratadine, 4231 (0.9%) had hypospadias. Women who used loratadine during pregnancy were not significantly more likely to have a son with hypospadias (unadjusted odds ratio [OR] 1.27, 95% CI 0.73, 2.23; adjusted OR 1.28, 95% CI 0.69, 2.39).

Conclusion: The results of our systematic review and meta-analysis of controlled observational studies indicate that the use of loratadine during pregnancy does not significantly increase the risk of hypospadias in male offspring.

Background

Allergic symptoms affect about one-third of women of childbearing age,[1] and frequently prompt use of medication during pregnancy.[2,3] First-generation antihistamines have long been used in the management of allergic symptoms and are considered safe for pregnant women.[4,5] Second-generation antihistamines, such as loratadine, cause less drowsiness because they do not cross the blood-brain barrier. Although the second-generation drugs are preferred by many individuals, the results of clinical and experimental studies have raised questions about whether they are safe for use during pregnancy.

In an epidemiological study in 2001, Swedish investigators reported that maternal use of loratadine was associated with an increased risk of hypospadias in male offspring.[6] Hypospadias is a birth defect in which the urethral meatus is located along the underside of the penis, scrotum or perineum. This condition, which usually requires surgical correction, is currently estimated to affect about 7 of every 1000 male infants born in the US.[7] It is also thought to be associated with gestational and pregestational diabetes mellitus,[8] increased maternal age[9] and *in vitro* fertilization.[10]

Researchers using animal models to evaluate the effect of loratadine on the development of androgen-dependent tissues have found mixed results. Using a rat model, investigators found that systemic loratadine exposure during the critical period of androgen-dependent development, at doses up to 26 times human exposure levels, did not result in malformations of androgen-dependent reproductive tissues in the male offspring.[11] However, in a study reported in 2006, pregnant mice exposed to loratadine syrup were found to have changes in steroid receptor messenger RNA expression profiles.[12] These changes were similar to changes elicited by a synthetic estrogen, and suggested a potential mechanism the for induction of hypospadias by loratadine.

Because it is important for clinicians who care for women of reproductive age to be able to summarize what is known about the association between loratadine and hypospadias, we performed a systematic review and meta-analysis of studies that have examined this topic in humans.

Methods

Data Sources

For our review and analysis, we followed the recommendations proposed by the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) Group.[13] Members of our team worked together to search the literature and to develop criteria for the inclusion of studies. We then worked independently in processes involving the selection of studies, the extraction of study data and the evaluation of methodology used in the studies. In each of these processes, we discussed disagreements until we reached a consensus.

With the assistance of a trained research librarian, we searched electronic databases for potentially pertinent articles that were published in any language from January 1989 (when loratadine became available) until May 2007. These databases included MEDLINE (via OVID), EMBASE, SCOPUS, TOXLINE Special (via Toxnet), DART: Developmental and Reproductive Toxicology, ReproTox, TERIS, OVID International Pharmaceutical Abstracts, CINAHL, Shepard's Citations, Google Scholar, Cochrane Library, World Cat, Digital Dissertations, Global Health, ISI Proceedings and BIOSIS Previews.

We began by using the ChemID database to identify synonyms of loratadine. In addition to searching the literature by drug names (loratadine, desloratadine, Claritin®, Clarityne®, Clarinase®,

cyproheptadine, registry number 79794-75-5), we searched by drug categories based on pharmacological action (antiallergic agents, antipruritics, histamine antagonists, second-generation antihistamines, histamine H1 antagonists, nonsedating). We combined these terms with various MeSH categories (including pregnancy, pregnancy complications, abnormalities, embryonic and fetal development, maternal exposure, teratogens, and congenital, hereditary and neonatal diseases and abnormalities) and keywords (including birth defect$, abnormalit$, hypospadia$, malformation$, fetal, pregnan$, deformit$ and embryopath$).

To find additional sources of published and unpublished data, we examined the bibliographies of the retrieved articles and also contacted six researchers in the field.

Study Selection

Studies were eligible for inclusion in our systematic review if they were cohort, case-control or case series studies that reported the incidence of hypospadias in the offspring of women who were or were not exposed to loratadine during pregnancy. A study was eligible for inclusion in both the systematic review and meta-analysis if it met the following additional criteria: (i) it reported odds ratios (ORs) or relative risks (RRs) and also reported a variance estimate or sufficient data to calculate one; and (ii) it reported data that were not included in a subsequent report by the same authors.

Manuscripts were excluded if they did not contain data about fetal outcomes following use of loratadine during gestation (e.g. studies of use of loratadine during lactation).

Two authors (EBS and MM) reviewed the studies to determine whether they met inclusion criteria. Three authors (EBS, SN and MM) then used a standardized data collection form to extract information concerning each study meeting the criteria. This information included article title, name of the first author, year of publication, study design, study location, characteristics and source of study population, sample size, outcome measures, and study methods for data collection, exposure measurement, ascertaining outcomes, blinding, handling loss to follow-up, and controlling for confounding factors. It also included unadjusted and adjusted RRs or ORs and their 95% confidence intervals (CIs) for hypospadias and other major fetal malformations associated with exposure to loratadine or other antihistamines. If the number of male births was not stated explicitly in published reports, we obtained this information from communication with authors. If we were unable to receive this information from authors, we assumed that 50% of births were male.

Two authors (EBS, SN) used the Newcastle-Ottawa Scale (NOS)[14] to assess the quality of the methodology used in the case-control and cohort studies. To rate the methods of selecting groups (cases and controls or exposed and non-exposed cohorts), we used a scale from 0 to 4, with 0 indicating the lowest quality. To rate the comparability of groups, we used a scale from 0 to 2 and awarded a study 1 point if it controlled for maternal age and 2 points if it controlled for maternal age and any additional factor. To rate the methods of ascertaining exposure or ascertaining outcome, we used a scale from 0 to 3, with 0 again indicating the lowest quality. We considered cohorts to have adequate follow-up if fewer than 10% of participants were lost to follow-up and if the loss occurred in a way that was unlikely to introduce bias.

From each study, we extracted data unadjusted for potential confounders, arranged them in a 2×2 table, and calculated the OR and corresponding standard error for the risk of hypospadias following exposure to loratadine. For studies with no events in one or both groups, a continuity correction of 0.5 was added to each cell (as implemented in Cochrane's Review Manager [RevMan; Cochrane Collaboration, Oxford, UK] version 4.2). When studies provided data about the risk of hypospadias following exposure to other antihistamines, these data were similarly abstracted. To generate a summary unadjusted OR for each type of exposure, we used the random-effects meta-analysis method of DerSimonian and Laird.[18] To generate a summary adjusted OR, we used the adjusted point estimates and standard errors extracted from each study.

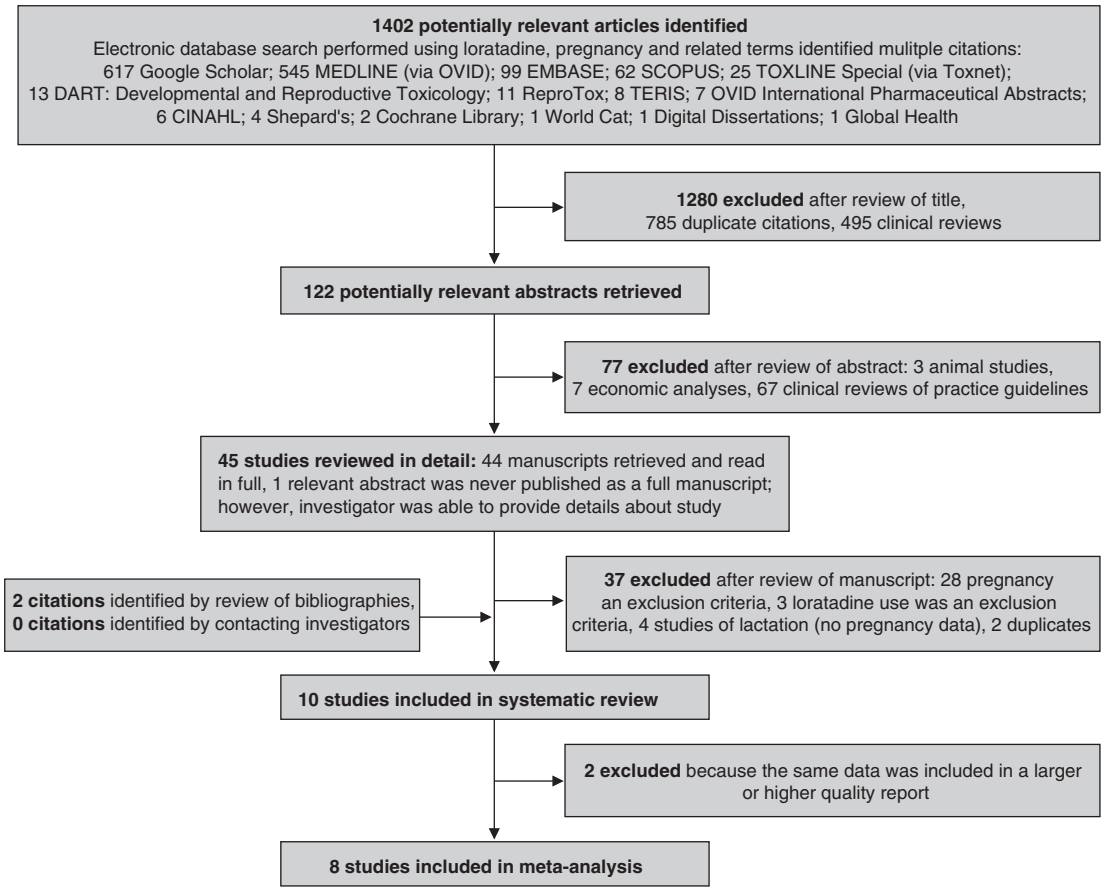

Fig. 1. Results of searches and screening of potentially relevant studies.

To determine whether results varied significantly by study design, we made separate analyses of case-control studies and cohort studies. In addition, we performed analyses with and without the hypothesis-raising Swedish study.[6]

For all statistical analyses, we used Cochrane's Review Manager version 4.2.

Results

Our literature search returned 1402 potentially relevant titles. After a review of titles, duplicates identified by different databases were removed. A total of 122 abstracts were retrieved for a more detailed review. The majority of these were subsequently excluded because they were clinical reviews without original data. Forty-four manuscripts were read in full; details of one additional study reported in abstract form[19] but never published as a manuscript, were provided by contacting the author (figure 1). Of these, three were reports of the same study[15,20,21] and ten met our criteria for inclusion in the systematic review.[5,6,15-17,19,22-25] However, two of the ten were later excluded[5,17] because they reported data that was contained in a larger or higher quality study.

Of the ten studies included in the systematic review, three were case-control studies (table I) and seven were cohort studies (table II). Study participants were from diverse geographic locations, including Brazil, Canada, Denmark, Israel, Italy, the UK and the US. However, the majority of subjects were Swedish. The three case-control studies de-

Table I. Characteristics of case-control studies identified by systematic review

Study and study period	Outcomes evaluated	No. of cases	No. of controls	Medication exposures studied	Data sources	Exposure period	Factors controlled or adjusted for	Population details
Werler et al.[15] Infants born 1/10/97 –30/6/01	Second- or third-degree hypospadias	558	1432	Loratadine; other nonsedating antihistamines; sedating antihistamines	Exposure determined via interviews with mothers; case/control infants identified through birth defect surveillance systems	From 1 mo pregestation through first 3 mo of pregnancy	Maternal age, race/ethnicity, state of residency at delivery, birth mo, family history of hypospadias	US infants who had English- or Spanish-speaking mothers and were identified by birth-defect surveillance systems in eight states
Pedersen et al.[16] 1998–2002	Hypospadias	203	2030	Loratadine; other antihistamines	Exposure determined from maternal questionnaires and telephone interviews; hypospadias cases identified via ICD codes listed in the nationwide hospital discharge registry	Women exposed from 30 d before conception through the end of the first trimester and women exposed at any time during pregnancy	Birth order, gestational age, maternal age, smoking, pre-eclampsia, use of ovulation-inducing drugs, antidiabetics, or antiepileptics	Danish infants and mothers who were listed in the nationwide hospital discharge registry
Pedersen et al.[17] 1989–2002	Hypospadias	227	2270	Loratadine; other antihistamines	Exposure determined via prescription records (dispensing information); hypospadias cases identified via ICD codes in the NHDR	Women who filled a prescription (i) 30 d pre-conception through end of first trimester; (ii) within the first 6 mo of pregnancy; and (iii) at any time during pregnancy	Maternal age, birth order, smoking, pre-eclampsia, diabetes mellitus, epilepsy and use of clomifene	Danish infants and mothers who were from four counties and were listed in the NHDR

ICD = International Classification of Diseases; **NHDR** = Nationwide Hospital Discharge Registry.

Table II. Characteristics of cohort studies identified by systematic review

Study and period	Outcomes evaluated	Live births to women using loratadine		Live births to women using other antihistamines	Live births to women not using antihistamines	Data sources	Exposure period	Factors examined or adjusted for	Population details
		all	male						
Wilton et al.[25] Prior to 1998	Live births (full-term or premature), stillbirths, abortions, intrauterine deaths, ectopic pregnancies, major and minor congenital anomalies	16	8[a]	37	540 in cohort for loratadine and 503 in cohort for any antihistamine	Exposure ascertained from prescription records; outcome assessment determined from patient's general practitioner	First trimester	None	UK women exposed to newly marketed drugs in whom pregnancy was recorded
Brown et al.[19] 1998	Birth weight, head circumference, length, Apgar scores, major malformation (including hypospadias)	51	25[a]	0	56	Exposure determined by prescribing clinician; outcomes assessed by medical record review	Pregnancy	None	Women seen at one US medical centre
Kallen and Olausson[6] Jul 1994–Dec 2001	Hypospadias	2 780	1 624[b]	5 116	298 754 M and 282 314 F[b]	Exposure ascertained from maternal interview; outcome assessed by record linkage (ICD codes)	Early pregnancy (first 10–12 wk)	Year of birth, maternal age, parity, smoking, use of other antihistamines	Women and infants in Sweden
Kallen[5] Jul 1995–Dec 2000	Hypospadias	1 755	916	16 442	387 103	Exposure ascertained from maternal interview; outcome assessed from record of attending physician	Early pregnancy (first 10–12 wk)	None	Women and infants in Sweden

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Table II. Contd

Study and period	Outcomes evaluated	Live births to women using loratadine		Live births to women using other antihistamines	Live births to women not using antihistamines	Data sources	Exposure period	Factors examined or adjusted for	Population details
		all	male						
Moretti et al.[24] 1997–2001	Major congenital malformations (including hypospadias), rates of miscarriage, birth weights, gestational age at delivery	140	73	0	149	Exposure ascertained by interview; outcome information verified by contacting child's physician	At least during first trimester (13 wk)	Maternal age, tobacco and alcohol use, gravidity, gestational age at interview, time of year	Women who were pregnant or planning pregnancy and contacted TIS (primarily in Canada, but also in Italy, Israel and Brazil)
Diav-Citrin et al.[22] 1995–2001	Rates of major anomalies; structural abnormalities serious medical, surgical or cosmetic consequences; live births, miscarriages, pregnancy terminations, stillbirths, ectopic pregnancies, and premature births; gestational age at delivery; birth weight	174	87[a]	239	819	Exposure and outcome ascertained from maternal interview	Any time during pregnancy; separate analysis also conducted for first trimester exposures	Maternal age, history of miscarriages, gestational age at time of contact or request for information	Pregnant women who contacted the Israeli TIS
Kallen and Olausson [23] 2002–4	Hypospadias	1 911	818[b]	NR	149 159 M and 140 906 F[b]	Exposure ascertained from maternal interview; outcome assessed from record of attending physician	Early pregnancy (first 10–12 wk)	Year of birth, maternal age, parity, smoking, use of other antihistamines	Women and infants in the Sweden

a Estimate based on assumption that half of the infants studied were male.

b Additional data provided by B. Kallen, personal communication (2006 Oct 25).

F = female; **ICD** = International Classification of Diseases; **M** = male; **NR** = not reported; **TIS** = Teratogen Information Service.

Table III. Evaluation of the quality of case-control studies identified by systematic review

Study	Selection of cases and controls (score 0–4)	Comparability of cases and controls (score 0–2)	Ascertainment of exposure (score 0–3)	Total (score 0–9)
Werler et al.[15]	4	2	2	8
Pedersen et al.[16]	3	2	3	8
Pedersen et al.[17]	3	2	2	7

scribed 785 distinct cases and at least 3702 controls. The exact number of controls is not known because two of the three studies[16,17] covered the same population and had overlapping timeframes. The seven cohort studies included 2635 women who used loratadine, and 446 248 women who did not use antihistamines who subsequently gave birth to a live male infant. Three of the seven cohort studies[5,6,23] covered the same population and had overlapping timeframes. To avoid the possibility of double counting when the same population was used in different studies, we selected the studies with the higher quality of methodology for this meta-analysis.

In half of the studies, information on maternal use of loratadine, hospitalization diagnoses and the presence of co-morbid states was determined from linked healthcare databases or electronic medical records that included hospital discharge diagnoses and prescription dispensing records. As in many countries, including Denmark, loratadine is available without a prescription, the remaining studies collected information through telephone-based structured interviews.

All ten studies reported on the relationship between loratadine and major fetal malformations or hypospadias, and seven of them also reported on the relationship between other antihistamines and these outcomes. In their estimates of the risk for adverse perinatal outcomes, all but three studies[5,19,25] adjusted for maternal age. In addition, some studies adjusted for paternal history of hypospadias, maternal tobacco use, maternal diabetes and other co-morbidities.

Each of the three case-control studies scored well across categories in the NOS and had a total score of 7 or 8 points out of a possible 9 (table III). The six cohort studies had component and total scores that were more variable, with total scores ranging from 5 to 9 points out of a possible 9 (table IV).

Together the studies included in the meta-analysis provided information about 453 107 male births. Of 2694 male infants born to women who used loratadine during pregnancy, 39 (1.4%) had hypospadias. Of 450 413 male infants born to women not using loratadine, 4231 (0.9%) had hypospadias (table V).

The summary unadjusted ORs (and 95% CIs) for hypospadias in offspring of women using loratadine versus women not using loratadine during pregnancy were 1.23 (0.62, 2.44) in the case-control studies, 1.13 (0.34, 3.81) in the cohort studies and 1.27 (0.73, 2.23) in all studies combined (table V and figure 2). When we repeated the meta-analysis of cohort studies without the hypothesis-generating study,[6] we found that the OR further approached

Table IV. Evaluation of the quality of cohort studies identified by systematic review

Study	Selection of exposed and non-exposed groups (score 0–4)	Comparability of groups (score 0–2)	Ascertainment of outcome (score 0–3)	Total (score 0–9)
Wilton et al.[25]	3	0	3	6
Brown et al.[19]	3	0	3	6
Kallen and Olausson[6]	4	2	3	9
Kallen[5]	4	0	3	7
Diav-Citrin et al.[22]	4	0	1	5
Moretti et al.[24]	4	2	2	8
Kallen and Olausson[23]	4	2	3	9

Table V. Results of case-control and cohort studies that examined hypospadias and exposure to loratadine

Study	With hypospadias[a]		Without hypospadias [a]		OR (95% CI)	
	exposed	unexposed	exposed	unexposed	unadjusted	adjusted
Case-control studies						
Werler et al.[15]	11	547	22	1 410	1.29 (0.62, 2.68)	0.96 (0.41, 2.22)
Pedersen et al.[16]	1	202	12	2 018	0.83 (0.11, 6.44)	0.90 (0.10, 6.90)
Pedersen et al.[17][b]	1	226	8	2 262	1.30 (0.00-9.30)	1.40 (0.00-10.50)
Summary ORs from case-control studies[c]					1.23 (0.62, 2.44)	0.95 (0.43, 2.08)
Cohort studies						
Wilton et al.[25]	0	1	8[d]	270[d]	10.61 (0.40, 279.84)	NR
Brown et al.[19]	0[e]	0[e]	25	28	Not estimable	NR
Kallen and Olausson (1995–2001)[6][f]	25[f]	2 586[f]	1 599[f]	294 544[f]	1.78 (1.20, 2.65)[f]	2.39 (1.43, 3.38)
Diav-Citrin et al.[22]	0	0	87[d]	409[d]	Not estimable[g]	Not reported
Moretti et al.[24]	0	1	73	68	0.31 (0.01, 7.76)	NR
Kallen and Olausson (2002–4)[23][f]	2[f]	894 [f]	816[f]	147 447[f]	0.40 (0.10, 1.62)[f]	0.47 (0.06, 1.68)
Summary ORs from cohort studies[c]					1.13 (0.34, 3.81)	1.23 (0.32, 4.69)
Summary ORs from case-control and cohort studies combined[c]					**1.27 (0.73, 2.23)**	**1.28 (0.69, 2.39)**

a Exposure 30 days before conception or in first trimester of gestation.

b Excluded from summary statistics, since the same cases are included in a higher quality study.

c Based on the use of a random-effects model.

d Based on the assumption that half of live births were male.

e Additional data provided by J.E. Brown, personal communication (2007 Mar 1). Unadjusted OR calculated by authors.

f Additional data provided by B. Kallen, personal communication (2006 Oct 25). Unadjusted OR calculated by authors.

g OR for any malformation reported as 0.77 (0.27, 2.19).

NR = not reported; **OR** = odds ratio.

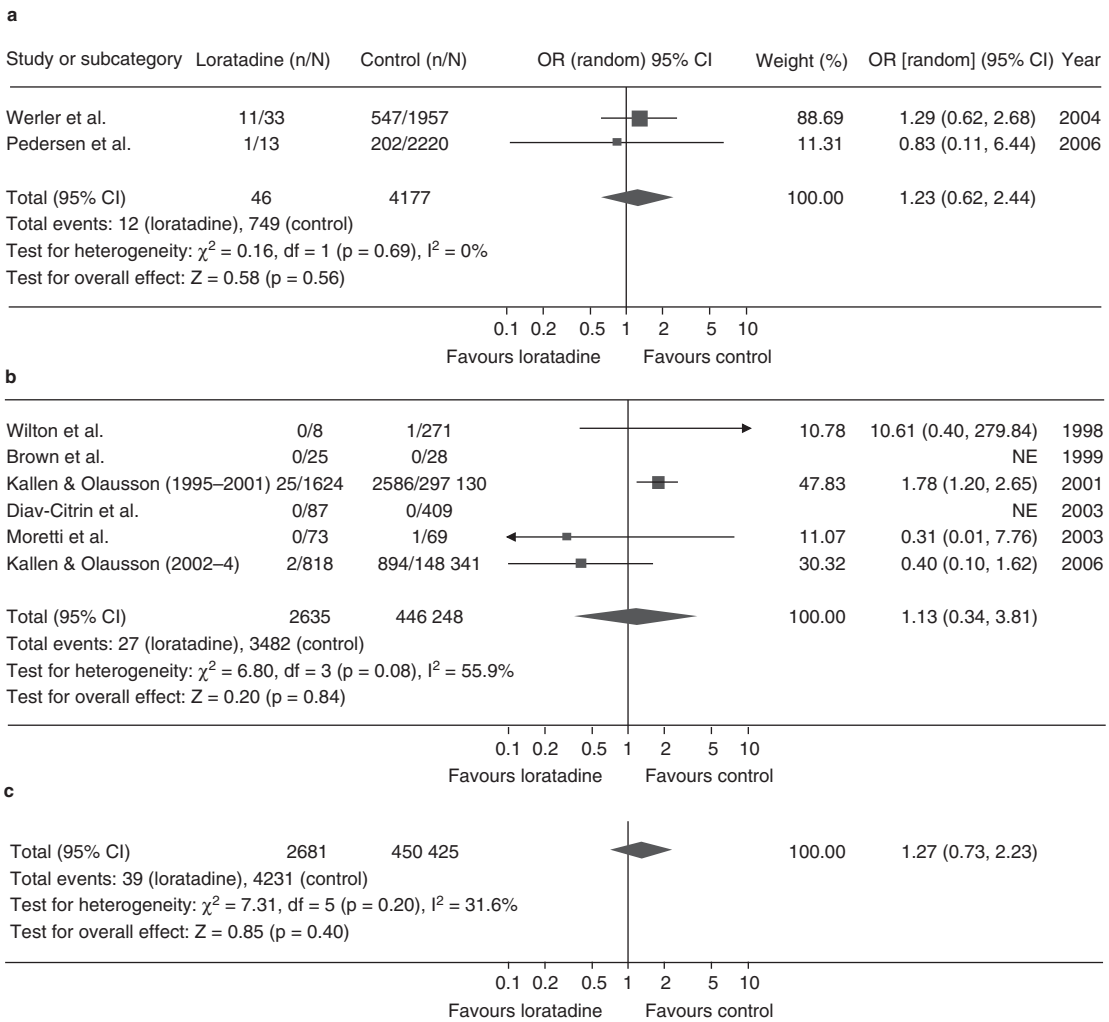

Fig. 2. Unadjusted odds ratios (ORs) and 95% CIs for hypospadias in offspring of women using loratadine vs women not using loratadine during pregnancy. Summary estimates are shown for (**a**) case-control studies;[15,16] (**b**) cohort studies;[6,19,22-25] and (**c**) all studies. **df** = degrees of freedom; **NE** = not estimable.

unity (OR 0.96; 95% CI 0.44, 2.08), and the degree of heterogeneity was lower as evidenced by an I^2 of 18% instead of 56%.

The summary adjusted ORs for hypospadias in offspring of women using loratadine versus women not using loratadine during pregnancy were 0.95 (95% CI 0.43, 2.08) in the case-control studies, 1.23 (0.32, 4.69) in the cohort studies and 1.28 (0.69, 2.39) in all studies combined (table V and figure 3). The summary obtained from all studies combined is higher than the estimate obtained from either methodological subset of studies because the relative weight assigned to each study differs on the basis of the size of the other studies included in the analysis.

The summary unadjusted OR for hypospadias in offspring of women using other antihistamines (i.e. antihistamines other than loratadine) versus women using no antihistamines was 1.02 (95% CI 0.71,

1.46) in the case-control studies, and the summary adjusted OR was 0.97 (0.66, 1.43) [figure 4].

Summary statistics were minimally different whether obtained by including all studies,[6,16,17,21-25] or after omitting studies that used the same population,[17,21-25] or after omitting studies that were of lower quality.[22,25]

Discussion

The results of our systematic review and meta-analysis of controlled observational studies indicate that the use of loratadine during pregnancy does not significantly increase the risk of hypospadias in male offspring.

Our results are not in keeping with the early findings of Kallen and Olausson,[6] which raised concern about the use of loratadine during pregnancy, but they are consistent with the 2006 findings of these same authors.[23] In their earlier study, when Kallen and Olausson examined the Swedish Medical Birth Registry and the Swedish Registry of Congenital Malformations, they found that hypospadias occurred in 0.54% of the offspring of mothers using loratadine versus the 0.20% they expected in a similar population.[6] They also found that hypospadias occurred in only 6 (0.11%) of 5116 infants born to mothers using antihistamines other than loratadine.[6] This led to concern that women who

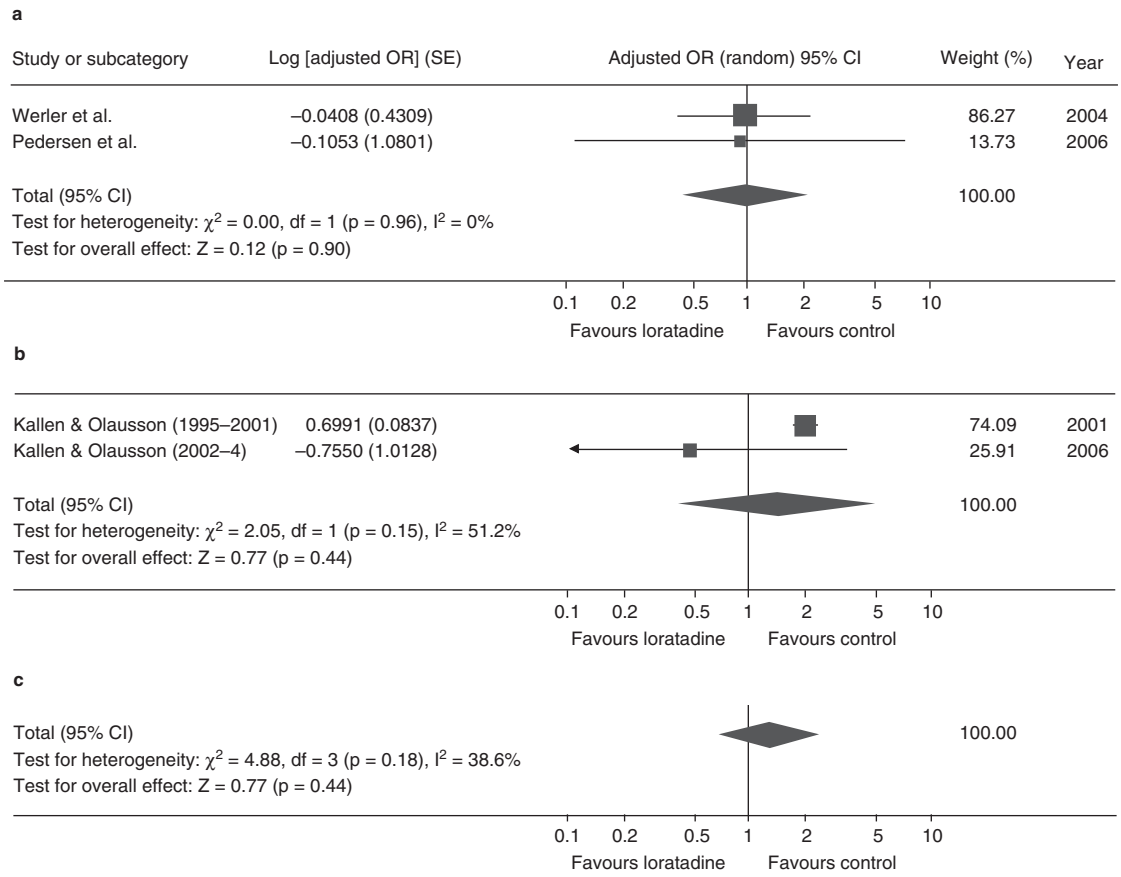

Fig. 3. Adjusted odds ratios (ORs) and 95% CIs for hypospadias in offspring of women using loratadine vs women not using loratadine during pregnancy. Summary estimates are shown for (**a**) case-control studies;[15,16] (**b**) cohort studies;[6,23] and (**c**) all studies. **df** = degrees of freedom; **SE** = standard error.

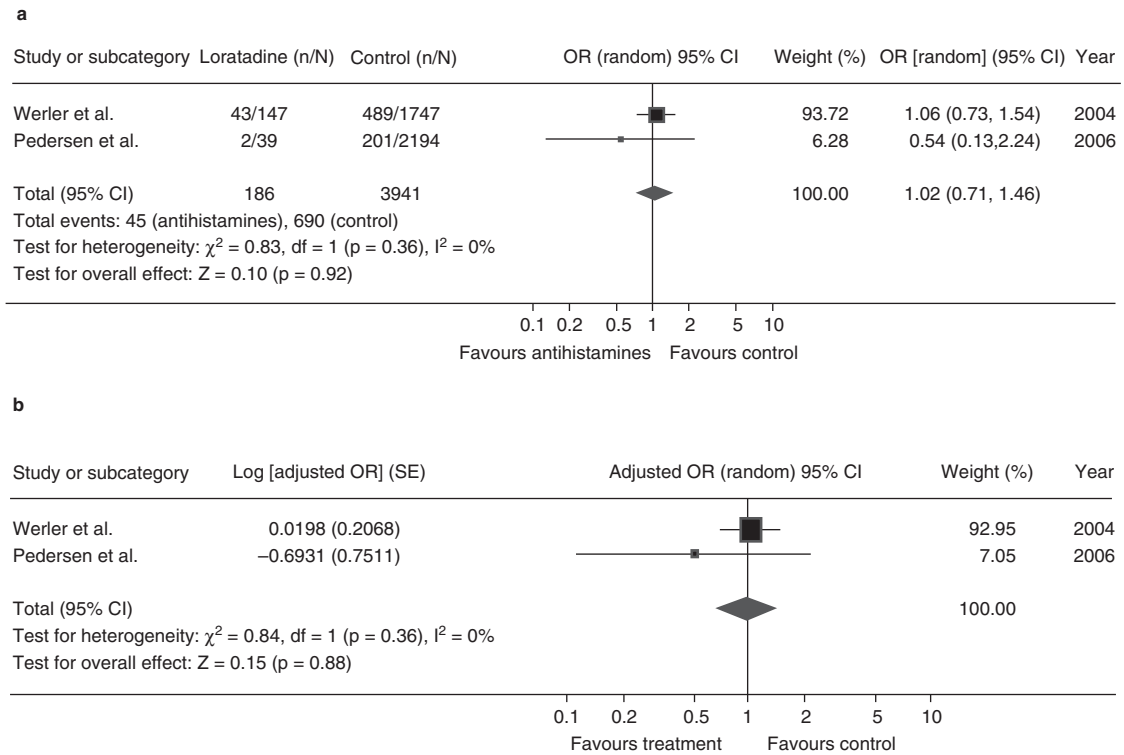

Fig. 4. Summary estimates of odds ratios (ORs) and 95% CIs for hypospadias in offspring of women using vs women not using antihistamines other than loratadine during pregnancy. (**a**) Unadjusted ORs and (**b**) adjusted ORs are for case-control studies.[15,16] **df** = degrees of freedom; **SE** = standard error.

used loratadine during pregnancy might be more likely than women who used other antihistamines during pregnancy to deliver a son with hypospadias. However, in 2006, these same authors examined updated information and found no increased risk of hypospadias with use of loratadine during pregnancy.[23]

The only other critical review[4] that examined a question similar to the one we examined was performed in 2005, prior to the publication of three of the larger studies included in this review. While prior reviews[26] have succeeded in reassuring many women and clinicians that first-generation antihistamines may be safely used during the first trimester of pregnancy, recommendations regarding use of second-generation antihistamines during pregnancy have remained guarded.[4] The findings of this study are reassuring in showing that data collected outside of Sweden supports conclusions of the more recent Swedish study.[23]

As is the case with the findings in other systematic reviews, the findings in our review are limited by the design and quality of the individual studies we included. Some studies in our review used databases that were not collected primarily for research. In this case, information on potential confounders was not always complete, and it is possible that adjustments for confounding were inadequate. A number of studies gathered data from large electronic databases or electronic medical records. The potential limitations of these studies are that the investigators use prescribing or dispensing as a proxy for drug consumption, that the records may misclassify clinical outcomes and co-morbid states, and that the records may have incomplete information regarding potential confounders, such as family

history, tobacco and alcohol use. However, the potential strengths of these studies are that selection and recall biases are minimized because drug exposure and outcomes are recorded prospectively, all eligible cases are available for inclusion, and controls are selected randomly from the source populations. In addition, the Pedersen et al.[16,17] studies included women who filled prescriptions for loratadine 30 days prior to conceiving, creating the possible risk of a misclassification of exposure, which would bias risk estimates towards 1. However, as allergic symptoms often persist for months at a time, we suspect that many women who filled prescriptions for loratadine the month before conception may have continued to use the medication at the time of organogenesis, minimizing the effect of this potential bias.

It is possible that our estimates of risk with maternal use of loratadine may be affected by selection bias. However, selection bias is less likely to affect between-drug comparisons (e.g. loratadine vs other antihistamines), and the risk of hypospadias following maternal use appears similar for loratadine and other antihistamines.

Conclusion

Data from controlled observational studies of fetal malformation do not indicate that the use of loratadine during pregnancy significantly increases the risk of hypospadias. While women have traditionally been counselled during pregnancy to treat allergic symptoms using first-generation antihistamines for which more clinical information is available, women who prefer to use loratadine and avoid the effects of sedating antihistamines can be reassured that using loratadine to control symptoms during pregnancy will not significantly increase the risk of hypospadias in their offspring.

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References

1. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf 1999; 20 (4): 361-75
2. Werler MM, Mitchell AA, Hernandez-Diaz S, et al. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol 2005; 193 (3 Pt 1): 771-7
3. Glover DD, Amonkar M, Rybeck BF, et al. Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. Am J Obstet Gynecol 2003; 188 (4): 1039-45
4. Gilbert C, Mazzotta P, Loebstein R, et al. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf 2005; 28 (8): 707-19
5. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002; 11 (3): 146-52
6. Kallen B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? Int J Risk Safety Med 2001; 14: 115-9
7. Gallentine ML, Morey AF, Thompson Jr IM. Hypospadias: a contemporary epidemiologic assessment. Urology 2001; 57 (4): 788-90
8. Aberg A, Westbom L, Kallen B. Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. Early Hum Dev 2001; 61 (2): 85-95
9. Fredell L, Kockum I, Hansson E, et al. Heredity of hypospadias and the significance of low birth weight. J Urol 2002; 167 (3): 1423-7
10. Wennerholm UB, Bergh C, Hamberger L, et al. Incidence of congenital malformations in children born after ICSI. Hum Reprod 2000; 15 (4): 944-8
11. McIntyre BS, Vancutsem PM, Treinen KA, et al. Effects of perinatal loratadine exposure on male rat reproductive organ development. Reprod Toxicol 2003; 17 (6): 691-7
12. Willingham E, Agras K, Vilela M, et al. Loratadine exerts estrogen-like effects and disrupts penile development in the mouse. J Urol 2006; 175 (2): 723-6
13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283 (15): 2008-12
14. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2006 [cited 2006 Nov 14]. OHRI [online]. Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.doc [Accessed 2006 Nov 14]
15. Werler M, McCloskey C, Edmonds L, et al. Evaluation of an association between loratadine and hypospadias: United States, 1997–2001. Arch Dermatol 2004; 140 (7): 893-4
16. Pedersen L, Norgaard M, Skriver MV, et al. Prenatal exposure to loratadine in children with hypospadias: a nested case-control study within the Danish National Birth Cohort. Am J Ther 2006; 13 (4): 320-4
17. Pedersen L, Skriver MV, Norgaard M, et al. Maternal use of loratadine during pregnancy and risk of hypospadias in offspring. Int J Med Sci 2006; 3 (1): 21-5
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7 (3): 177-88

19. Brown JE, Stern H, Leeds T. Loratadine and pregnancy: outcomes in 49 pregnancies. Allergy Asthma Proc 1999; 20 (3): 199-200
20. Werler M, McCloskey C, Edmonds L, et al. Evaluation of an association between loratadine and hypospadias: United States, 1997–2001. JAMA 2004; 291 (15): 1828-30
21. Werler M, McCloskey C, Edmonds L, et al. Evaluation of an association between loratadine and hypospadias: United States, 1997–2001. MMWR Morb Mortal Wkly Rep 2004; 53 (10): 219-21
22. Diav-Citrin O, Shechtman S, Aharonovich A, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. J Allergy Clin Immunol 2003; 111 (6): 1239-43
23. Kallen B, Olausson PO. No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy. Int J Med Sci 2006; 3 (3): 106-7
24. Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. J Allergy Clin Immunol 2003; 111 (3): 479-83
25. Wilton LV, Pearce GL, Martin RM, et al. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol 1998; 105 (8): 882-9
26. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol 1997; 14 (3): 119-24

Correspondence: Dr *Eleanor B. Schwarz*, Assistant Professor of Medicine, Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, Center for Research on Health Care, 230 McKee Place, Suite 600, Pittsburgh, PA 15213, USA.
E-mail: schwarzeb@upmc.edu