Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis

Schwarz E B, Moretti M E, Nayak S, Koren G

CRD summary

The review concluded that the use of loratadine (a second generation antihistamine) during pregnancy did not significantly increase the risk of hypospadias in male offspring. This seems to be a reasonable interpretation of the evidence and the authors' conclusion is likely to be reliable.

Authors' objectives

To determine the risk of hypospadias (congenital defect in the position of the urethra opening on the penis) in male offspring of women who received loratadine (a second generation antihistamine) during pregnancy.

Searching

The following databases were searched from January 1989 to May 2007: MEDLINE, EMBASE, SCOPUS, TOXLINE Special, CINAHL, The Cochrane Library, Developmental and Reproductive Toxicology (DART), REPROTOX, TERIS, International Pharmaceutical Abstracts (IPA), BIOSIS Previews, ISI Proceedings, Shepard's Citations, World Cat, Digital Dissertations, Global Health and Google Scholar. Details of the search strategy were reported. Authors in the field were contacted and references of retrieved articles were checked in order to locate any additional papers.

Study selection

Cohort studies, case control or case-series reporting the incidence of hypospadias in the offspring of women who were or were not exposed to loratadine during pregnancy were eligible for inclusion in the review. Studies that did not report data on foetal outcomes following the use of loratadine during gestation were excluded.

Loratadine use was determined from linked healthcare databases, electronic medical records or, where loratadine is available without prescription, through telephone-based structured interviews. Exposure to loratadine was recorded from one month before conception up to end of pregnancy, although the majority of studies considered only the first trimester. Prescribing or dispensing was used as a proxy measure of drug consumption in a number of the included studies. All studies reported on major foetal malformations or hypospadias. Some studies reported a number of additional pregnancy and perinatal outcomes.

Two reviewers selected studies for inclusion in the review. Disagreements were resolved through discussion.

Assessment of study quality

Methodological quality was assessed using the Newcastle-Ottawa Scale. Criteria included: selection of exposed and non-exposed groups; comparability of groups and ascertainment of outcome in the cohort studies and selection of cases and controls;, comparability of cases and controls; and ascertainment of exposure for the case-control studies. A maximum possible score of 9 could be obtained.

Two reviewers assessed the methodological quality of the included studies.

Data extraction

Unadjusted and adjusted relative risks (RRs) and odds ratios (ORs) were extracted, with their 95% confidence intervals (CIs), for hypospadias and other foetal malformations associated with exposure to loratadine or other antihistamines. Unadjusted ORs were calculated by extracted 2x2 data. Adjusted point estimates and standard errors were extracted from each study in order to calculate summary adjusted OR. For studies with no events in one or both groups a continuity correction of 0.5 was added to each cell. The number of male births was also recorded. If this information was unavailable from the paper or the authors, then it was assumed that 50% of births were male.

Three reviewers extracted data onto a standardised form and any disagreements were resolved through discussion.

Methods of synthesis
Unadjusted and adjusted ORs were pooled using a random-effects model. Data were pooled separately for cohort and case-control studies and with/without one cohort study thought to differ from the other studies. Statistical heterogeneity was assessed using the χ^2 test and the I^2 statistic.

Results of the review
Ten studies were included in the systematic review; three case controls (988 cases and 5,732 controls) and seven cohort studies (n=1,288,964). However, two case control studies and three cohort studies covered the same populations and had overlapping time frames, thus the actual number of unique cases was 785 and at least 3,702 controls (case-controls) and 2,635 women who used loratadine and 446,248 women who did not use antihistamines (cohort studies). Scores on the Newcastle-Ottawa Scale ranged from 7 to 8 on the case control studies and 5 to 9 on the cohort studies. Two studies (one case control and one cohort study) were excluded from the analysis due to duplicate data. Two publications related to the same cohort study were included in the meta-analysis as they contributed data for non-overlapping time points. In total, eight studies were included in the meta-analysis (453,107 male births).

Of 2,694 male infants born to women who were exposed to loratadine during pregnancy, 1.4% (39 infants) had hypospadias. Of 45,413 male infants born to women not exposed to loratadine during pregnancy, 0.9% (4,231 infants) had hypospadias. No statistically significant difference was found for the odds of hypospadias in the offspring of women using loratadine during pregnancy compared with women not exposed to loratadine during pregnancy (unadjusted OR 1.27, 95% CI: 0.73, 2.23, I^2=31.6%; adjusted OR 1.28, 95% CI: 0.69, 2.39, I^2=38.6%), based on eight studies. Results were similar when stratified according to study design, after omitting studies that used the same population and those of poorer quality. No increased risk of hypospadias was found in offspring of women using other antihistamines compared with women using no antihistamines, based on two studies.

Authors' conclusions
Results from controlled observational studies suggest that the use of loratadine during pregnancy did not significantly increase the risk of hypospadias in male offspring.

CRD commentary
The review was supported by clear inclusion criteria in terms of study design, population and intervention. Several databases were searched and the authors attempted to locate unpublished literature, minimising the likelihood of publication bias. While multiple reviewers were involved in the process of study selection, data extraction and validity assessment, the authors did not state whether reviewers carried out these procedures independently. Consequently, the possibility of reviewer error or bias at these stages could not be ruled out.

Methodological quality of the included studies was assessed using a standardised scale. Summary results were reported for each study. The decision to use a meta-analysis appeared appropriate, as did the methods used for the exploration of statistical heterogeneity.

The authors' conclusion seems to be a reasonable interpretation of the evidence presented and is likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that women who prefer to use loratadine during pregnancy and avoid the effects of sedating antihistamines could be reassured that it would not significantly increase the risk of hypospadias in their offspring.

Research: The authors did not state any implications for research.

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