Original Article

Desloratadine Use During Pregnancy and Risk of Adverse Fetal Outcomes: A Nationwide Cohort Study

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What is already known about this topic? Desloratadine is a frequently used second-generation antihistamine, but the fetal safety of desloratadine use during pregnancy has not been previously examined.

What does this article add to our knowledge? This nationwide cohort study included all pregnancies with the use of desloratadine during pregnancy in Denmark from 2001 through 2016 and found no association between desloratadine and adverse fetal outcomes as compared with the use of loratadine. Comparison with additional comparator groups showed similar results.

How does this study impact current management guidelines? These results provide reassurance by indicating that the fetal safety of desloratadine is similar to the currently recommended second-generation antihistamines during pregnancy, and thus can be used equally.

BACKGROUND: Desloratadine is a frequently used drug for the treatment of allergic disorders, which often also require treatment during pregnancy. However, information on the fetal safety of desloratadine use during pregnancy is limited.
OBJECTIVE: To investigate the association between desloratadine use during pregnancy and adverse fetal outcomes.
METHODS: From a cohort of 1,287,668 pregnancies identified in the Danish nationwide registries in the study period 2001 to 2016, users of desloratadine and loratadine during pregnancy were matched in a 1:1 ratio based on propensity scores to compare the risk of adverse fetal outcomes. We compared the risk of the primary outcomes major birth defects (among a total of 3348 pregnancies) and spontaneous abortion (5498 pregnancies) and the secondary outcomes preterm birth (5280 pregnancies), small size for gestational age (SGA) for birth weight (5436 pregnancies), and stillbirth (6776 pregnancies). Logistic regression was used to estimate the prevalence odds ratio (OR) of major birth defects, preterm birth, and SGA, and Cox regression to estimate the hazard ratio (HR) of spontaneous abortion and stillbirth. Sensitivity analyses included comparing with cetirizine use in pregnancy and with pregnancies unexposed to desloratadine but with prior use as additional comparator groups.
RESULTS: Use of desloratadine in pregnancy was not associated with a significant increased risk of major birth defects (prevalence OR, 1.07; 95% confidence interval [CI], 0.77-1.50), spontaneous abortion (HR, 1.15; 95% CI, 0.96-1.37), preterm birth (prevalence OR, 0.84; 95% CI, 0.67-1.05), SGA (prevalence OR, 0.97; 95% CI, 0.80-1.16), or stillbirth (HR, 0.91; 95% CI, 0.31-2.70) compared with loratadine use in pregnancy. Sensitivity analyses, including those with the use of additional comparator groups, showed similar results.
CONCLUSION: Use of desloratadine during pregnancy was not associated with a statistically significant increased risk of adverse fetal outcomes as compared with loratadine. Results indicate that the fetal safety profile of desloratadine is similar to the currently recommended second-generation antihistamines during pregnancy. **© 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Desloratadine; Pregnancy; Adverse fetal outcomes; Propensity score–matched design; Nationwide cohort study*

Desloratadine is a second-generation antihistamine, part of first-line therapy, and frequently used for the treatment of allergic disorders such as allergic rhinitis and urticaria.[1-3] Allergic disorders are estimated to affect 20% to 30% of women of childbearing age, and antihistamines are one of the most frequently prescribed drugs during pregnancy, reported to be prescribed up to one in every seventh pregnancy.[4-6]

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Abbreviations used
ATC- Anatomic therapeutic chemical
CI- Confidence interval
EUROCAT- European Surveillance of Congenital Anomalies
HR- Hazard ratio
OR- Odds ratio
SGA- Small size for gestational age

Data to support the fetal safety of desloratadine use during pregnancy are lacking. Although no studies, to our knowledge, have previously investigated the use of desloratadine in pregnancy, fetal safety studies of loratadine, in which desloratadine is the main active metabolite, found no risk of adverse fetal outcomes with the use of loratadine during pregnancy and is considered as safe.[4,7-11]

Despite the pharmacological similarities, concerns exist regarding if the fetal safety assessment of loratadine can be extrapolated to desloratadine.[2,12] The risk summary of the use of desloratadine in pregnancy in the product label states that the limited data in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage.[13] In addition, current guidelines recommend the use of loratadine or cetirizine in pregnancy when treatment with a second-generation antihistamine is needed.[2,6,14,15]

Thus, existing data are inadequate to evaluate the potential fetal risk of desloratadine use in pregnancy. Given the prevalent use and proven effectiveness of desloratadine to treat allergic disorders, this issue emerges as of substantial clinical importance.[14,16] In a nationwide cohort study, we investigated the association between desloratadine use during pregnancy and adverse fetal outcomes. With the use of a propensity score–matched design, we matched desloratadine use with loratadine use during pregnancy as an active comparative group for the primary analyses. Primary outcomes were major birth defects and spontaneous abortions and secondary outcomes were preterm birth, small size for gestational age (SGA) for birth weight, and stillbirth. The association between desloratadine and primary outcomes was secondly examined in sensitivity analyses according to additional comparator groups of cetirizine use in pregnancy and pregnancies unexposed to desloratadine but with prior use as well as different exposure definitions.

METHODS

Data sources and study cohort

On the basis of nationwide registries, we linked individual-level data from different registries by using the unique personal identification number that is assigned to all inhabitants of Denmark. From the Medical Birth Registry and the National Patient Registry, we identified the source population that included all pregnancies that resulted in either live birth or fetal death (ie, abortive outcome and stillbirth) in the study period January 1, 2001, until December 31, 2016.[17,18] All live and stillbirths pregnancies are registered in the Medical Birth Registry (ever since 1978), whereas all pregnancies with abortive outcomes are registered in National Patient Registry and since 1997 also holding information on date of conception and abortion. Information on prescribed drug utilization was obtained from the Registry of Medicinal Product Statistics, which holds information on all redeemed prescriptions from all Danish pharmacies, and information on demographic variables was obtained from the Danish Civil Registration System and Statistics Denmark.[19,20] All registries are continuously updated. A detailed description of the utilized registries is provided in the Methods section of this article's Online Repository at www.jaci-inpractice.org.

For analyses of major birth defects, preterm birth, and SGA for birth weight, only pregnancies that resulted in live births were included, whereas all pregnancies were included for the analyses of fetal death. We followed the cohort from pregnancy onset (ie, first day of the last menstrual period) by obtaining gestational age registered at the date of birth or abortive outcome. Pregnancies with multiple records on overlapping dates and pregnancies with implausible or missing information on gestational age were excluded. Additional exclusion criteria were applied for the specific outcome analyses of major birth defects, exclusion of infants with birth defects due to chromosomal aberrations, genetic syndromes, and malformation syndromes of known causes as well as exclusion of pregnancies with missing information on birth weight for the analysis of SGA for birth weight.

Desloratadine exposure

Exposure was defined as at least 1 filled prescription of desloratadine identified through the Registry of Medicinal Product Statistics (anatomic therapeutic chemical [ATC]: R06AX27). The exposure time window of interest was defined in relation to the specific outcome analyses: the first trimester for the analysis of major birth defects; before 37 completed gestational weeks for preterm birth; before gestational week 23 for spontaneous abortion; and any time in pregnancy for SGA for birth weight and stillbirth. We allowed women with filled prescriptions during the 30 days before conception to be included in the cohort for all analyses. Pregnant women with filled prescriptions of loratadine (ATC: R06AX13) consisted as the active comparative reference group. Pregnant women with filled prescriptions of cetirizine (ATC: R06AE07) were used as a second active comparator group in sensitivity analyses of primary outcomes. We excluded pregnancies in case of concurrent use of desloratadine and the comparative drug within the same pregnancy.

Outcomes

We identified outcome cases diagnosed via inpatient or outpatient care registered in the National Patient Registry and the Medical Birth Registry. The primary outcomes were any major birth defects diagnosed within the first year of life and spontaneous abortion, that is, fetal death before 22 completed gestational weeks. We defined cases of major birth defects according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system of subgroups of major congenital anomalies and excluded minor defects according to the EUROCAT exclusion list.[21] We defined cases of spontaneous abortion as a pregnancy with an International Classification of Disease version 10 code of O021 or O03 diagnosed after 5 completed gestational weeks (due to the risk of misclassification of very early spontaneous abortions). Secondary outcomes were preterm birth (defined as delivery before 37 completed gestational weeks), SGA for birth weight (defined as lowest 10th percentile of the gestational age-specific birth weight within the source cohort), and stillbirth (defined as fetal death later than 22 completed gestational weeks). Further details on outcome definitions are provided in the Methods section of this article's Online Repository at www.jaci-inpractice.org.

Covariates

Propensity score matching was used to control for potential confounders. We performed separate propensity score matching for each individual outcome analysis. Pregnant women with

desloratadine use were matched in a 1:1 ratio with loratadine use. A logistic regression model was used to estimate propensity scores, which estimates the probability of desloratadine use during pregnancy based on a broad range of baseline characteristics at pregnancy onset (unless otherwise stated) as predictors, which included demographic variables, previous pregnancy outcomes, and prescription drug use as well as hospital care utilization in the past year before conception (see Table E1 in this article's Online Repository at www.jaci-inpractice.org for the specific definitions of all included covariates).

Statistical analysis

Based on individual propensity score matching, 5 pairwise matched cohorts were established for the primary analyses. We imputed missing values (0%-2.6% missing, see Table E2 in this article's Online Repository at www.jaci-inpractice.org) using the mode value. Matching was performed using the greedy nearest-neighbor matching algorithm (caliper width 0.02 on the propensity score scale).[22,23] Balance of covariates between matched groups was assessed by the standardized differences. A covariate was considered well balanced if the standardized difference was below 10%.

For the analyses of major birth defects, preterm birth, and SGA for birth weight, we used a logistic regression model to estimate prevalence odds ratios (OR). For the analyses of spontaneous abortion and stillbirth, we used the Cox proportional-hazards regression model to estimate hazard ratios (HR). Gestational age (in days) served as the underlying time scale. Censoring of a pregnancy occurred in case of another abortive outcome event other than the outcome of interest. The proportional hazard assumption was assessed using a Wald test for the interaction between time scale and exposure. All measures of associations were reported with the corresponding 95% confidence intervals (CIs). Statistical tests were 2-sided; CIs that did not overlap 1.0 were considered to indicate statistical significance.

We performed several preplanned sensitivity analyses of the association between desloratadine use and primary outcomes. These included comparing with pregnancies with the use of cetirizine as a secondary active comparator; comparing with women with filled prescriptions for desloratadine from 6 months before pregnancy up until 30 days before their pregnancy onset (but not during pregnancy); categorizing 1 or 2 or more filled prescriptions for desloratadine; restricting to pregnancies with filled prescriptions after pregnancy onset only; restricting to singleton pregnancies only and first-time pregnancies only for the analysis of major birth defects; comparing pregnancies with filled prescriptions for desloratadine or loratadine at any time throughout the entire pregnancy for the analysis major birth defects; and an analysis of the risk of induced abortions. In a *post hoc* analysis, we examined the association according to the timing of induced abortion, before or after the end of gestational week 12, and the risk of birth defects among pregnancies with induced abortion to investigate if birth defects were the reason for terminating the pregnancy.

SAS software 9.4 was used for all analyses. The study was approved by the Danish Data Protection Agency. Register-based research does not require ethical approval in Denmark.

RESULTS

Cohort selection

We identified 1,287,668 pregnancies eligible for study inclusion during the study period 2001 to 2016. After the use of the respective inclusion and exclusion criteria for each individual outcome analysis, propensity score matching subsequently established the 5 study cohorts (see Figure 1). Tables E3 and E4 (available in this article's Online Repository at www.jaci-inpractice.org) present the characteristics for the unmatched cohorts. The matched cohort included a total of 3348 pregnancies (with the use of either desloratadine or loratadine in a 1:1 ratio) for the analyses of major birth defects, 5498 pregnancies for spontaneous abortion, 5280 pregnancies for preterm birth, 5436 pregnancies for SGA for birth weight, and 6776 pregnancies for the stillbirth analysis. Baseline characteristics were well balanced between the groups for all matched cohorts, with standardized differences below 10% and nicely weighted (see Table I and Tables E5-E7, available in this article's Online Repository at www.jaci-inpractice.org). The proportional hazard assumption was fulfilled for all analyses on fetal death.

Primary and secondary outcomes

Table II reports the associations between desloratadine use in pregnancy and primary and secondary outcomes compared with loratadine use in pregnancy. Infants with major birth defects were diagnosed in 76 (4.5%) pregnancies with the use of desloratadine compared with 71 (4.2%) pregnancies with the use of loratadine during the first year of life (prevalence OR, 1.07; 95% CI, 0.77-1.50). Spontaneous abortions occurred in 256 (9.3%) pregnancies with the use of desloratadine and 230 (8.4%) with the use of loratadine (HR, 1.15; 95% CI, 0.96-1.37). For the analyses of the secondary outcomes, there were no significant increased risk of preterm birth (prevalence OR, 0.84; 95% CI, 0.67-1.05), SGA for birth weight (prevalence OR, 0.97; 95% CI, 0.80-1.16), and stillbirth (HR, 0.91; 95% CI, 0.31-2.70) for desloratadine use in pregnancy compared with loratadine use.

Sensitivity analyses

Table III reports results from the sensitivity analyses according to different definitions of exposure including the use of additional comparator groups and the association with the primary outcomes. For the sensitivity analyses of major birth defects, there were no significant differences in the risk between desloratadine use compared with cetirizine use in first trimester (prevalence OR, 1.36; 95% CI, 0.96-1.91; see Tables E8 and E9 in this article's Online Repository at www.jaci-inpractice.org) and desloratadine use in first trimester compared with pregnancies with desloratadine use 6 months before pregnancy only (prevalence OR, 1.00; 95% CI, 0.69-1.45). Sensitivity analyses of the risk of major birth defects when excluding pregnancies with filled prescriptions in the 30 days before pregnancy onset, restricting to singleton pregnancies only, restricting to first-time pregnancies only, and extending the exposure period throughout the entire pregnancy provided similar results (see Table E10 in this article's Online Repository at www.jaci-inpractice.org).

For the sensitivity analyses of spontaneous abortion, no significant differences in the risk were found between: desloratadine use compared with cetirizine use in pregnancy (HR, 1.04; 95% CI, 0.87-1.24) and desloratadine use in pregnancy compared with pregnancies with desloratadine use 6 months before pregnancy only (HR, 0.84; 95% CI, 0.67-1.04). No differences in the estimates of spontaneous abortion were identified in the sensitivity analyses when excluding pregnancies with filled prescriptions in the 30 days before pregnancy onset (see Table E10 in this article's Online Repository at www.jaci-inpractice.org).

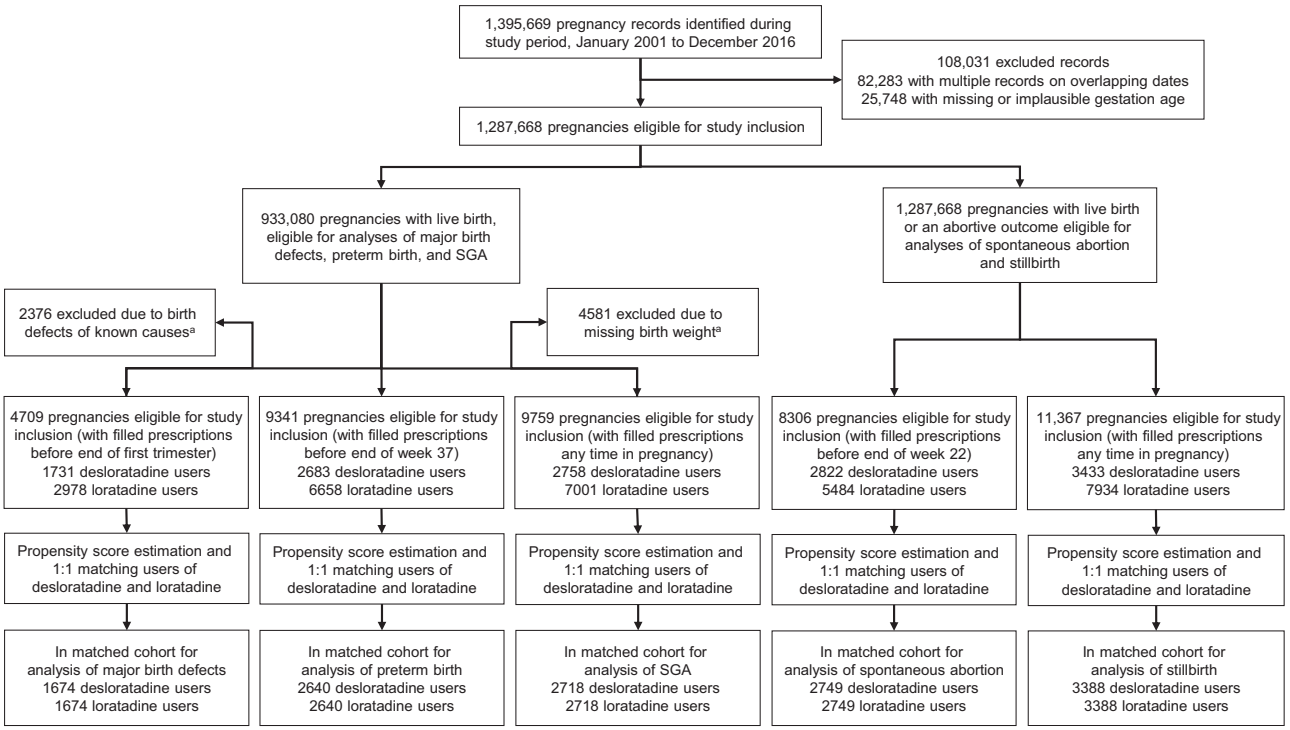

FIGURE 1. Flowchart of the study design. Selection of study cohorts for comparison of desloratadine use and loratadine use in pregnancy. *SGA*, Small size for gestational age for birth weight. [a]The excluded pregnancies were identified within the cohort of 933,080 live birth pregnancies.

For the analyses according to the number of filled prescriptions for desloratadine (1 or 2 or more filled prescriptions), no statistically significant increased risk was identified among pregnancies with 2 or more filled prescriptions of desloratadine for both major birth defects and spontaneous abortion.

A significant association was found between desloratadine use and induced abortion compared with loratadine use in pregnancy (see Table E10 in this article's Online Repository at www.jaci-inpractice.org); thus, we subsequently performed *post hoc* analyses, where the association was examined according to the timing of induced abortion (before or after the end of gestational week 12) and the risk of birth defect cases among induced abortions. Compared with loratadine, desloratadine use in pregnancy was significantly associated with induced abortion before 12 completed gestational weeks (HR, 1.34; 95% CI, 1.14-1.57), comprising 92.7% of all cases of induced abortions. No significant association between desloratadine use and induced abortion later than gestational week 12 (HR, 1.24; 95% CI, 0.70-2.19) or cases of birth defects among induced abortions (prevalence OR, 0.77; 95% CI, 0.29-2.06) were identified compared with loratadine use in pregnancy.

DISCUSSION

In this nationwide cohort study, desloratadine use in pregnancy was not associated with a significantly increased risk of adverse fetal outcomes as compared with loratadine use. Up to 3388 pregnancies with the use of desloratadine during pregnancy were included to investigate the risk of major birth defects, spontaneous abortion, preterm birth, SGA for birth weight, and stillbirth while comparing with matched pregnancies with the use of loratadine. Preplanned sensitivity analyses, comparing desloratadine use with cetirizine use in pregnancy and with pregnancies unexposed to desloratadine but with prior use, showed similar results to those of the main analyses.

Although previous data do not suggest an increased risk of adverse fetal outcomes with loratadine (desloratadine is the main active metabolite of loratadine) use in pregnancy, concerns exist regarding that the fetal safety assessment of loratadine may not be applicable to desloratadine.[7,8,12] We are not aware of any data previously investigating the individual association between desloratadine use in pregnancy and adverse fetal outcomes. Present findings thus provide clinically relevant and needed data to evaluate the fetal safety of desloratadine use in pregnant women. We found no significant differences in the risk of major birth defects or spontaneous abortion between desloratadine use in pregnancy compared with the currently recommended second-generation antihistamines during pregnancy, namely loratadine and cetirizine.

Findings from previous cohort studies did not suggest an association between loratadine use in pregnancy and spontaneous abortion, preterm, lower birth weight, or stillbirth although sample sizes were small.[10,11] Our estimates among the pregnancies with loratadine use are somewhat consistent with those from previous studies. We report original data on a large number of included pregnancies, finding no association between desloratadine use in pregnancy and risk of adverse fetal outcomes. Furthermore, because desloratadine and loratadine share several pharmacological properties, a null-finding for such comparison may be ascribed to a similar mechanism of action. However, we performed several sensitivity analyses including the use of

TABLE I. Baseline characteristics of propensity score–matched pregnancy cohorts of desloratadine and loratadine users in a 1:1 ratio. Data are represented as n (%)

	Matched cohort for analysis of major birth defects		Matched cohort for analysis of spontaneous abortion	
Characteristics	**Desloratadine users (n = 1674)**	**Loratadine users (n =1674)**	**Desloratadine users (n = 2749)**	**Loratadine users (n = 2749)**
Age at pregnancy onset				
≤19	21 (1.3)	25 (1.5)	91 (3.3)	99 (3.6)
20-24	151 (9.0)	150 (9.0)	284 (10.3)	302 (11.0)
25-29	495 (29.6)	486 (29.0)	771 (28.1)	789 (28.7)
30-34	629 (37.6)	617 (36.9)	942 (34.3)	913 (33.2)
≥35	378 (22.6)	396 (23.7)	661 (24.1)	646 (23.5)
Married or living with partner	1448 (86.5)	1451 (86.7)	2240 (81.5)	2241 (81.5)
Place of birth				
Denmark	1411 (84.3)	1422 (85.0)	2317 (84.3)	2326 (84.6)
Europe	88 (4.9)	82 (4.9)	132 (4.8)	136 (5.0)
Outside of Europe	175 (10.5)	170 (10.2)	300 (10.9)	287 (10.4)
Region of residence				
Capital	548 (32.7)	573 (34.2)	1317 (47.9)	1329 (48.3)
Sealand	263 (15.7)	276 (16.5)	337 (12.3)	325 (11.8)
Southern Denmark	334 (20.0)	311 (18.6)	425 (15.5)	432 (15.7)
Mid Jutland	365 (21.8)	356 (21.3)	466 (17.0)	456 (16.6)
North Jutland	164 (9.8)	158 (9.4)	204 (7.4)	207 (7.5)
Gross household income (quartile)				
1	446 (26.6)	448 (26.8)	744 (27.0)	785 (28.5)
2	390 (23.3)	369 (22.0)	652 (23.7)	602 (21.9)
3	395 (23.6)	409 (24.4)	647 (23.5)	641 (23.3)
4	443 (26.5)	448 (26.8)	708 (25.7)	723 (26.3)
Education level (y)				
≤11	329 (19.7)	329 (19.7)	666 (24.2)	669 (24.3)
12-13	232 (13.9)	209 (12.5)	399 (14.5)	411 (15.0)
14-15	398 (23.8)	402 (24.0)	611 (22.2)	563 (20.5)
≥16	715 (42.7)	734 (43.9)	1073 (39.0)	1106 (40.2)
Parity				
1	803 (48.0)	798 (47.7)	NA	NA
2	551 (32.9)	573 (34.2)	NA	NA
≥3	320 (19.1)	303 (18.1)	NA	NA
Multiple birth pregnancy	71 (4.2)	56 (3.4)	NA	NA
Season of conception				
Winter	280 (16.7)	290 (17.3)	610 (22.2)	582 (21.2)
Spring	613 (36.6)	600 (35.8)	956 (34.8)	984 (35.8)
Summer	525 (31.4)	523 (31.2)	755 (27.5)	761 (27.7)
Autumn	256 (15.3)	261 (15.6)	428 (15.6)	422 (15.4)
Smoking during pregnancy	175 (10.5)	171 (10.2)	NA	NA
Previous pregnancy with the same adverse fetal outcome	30 (1.8)	28 (1.7)	343 (12.5)	349 (12.7)
Previous pregnancy with induced abortion	NE	NE	318 (11.6)	305 (11.1)
Prescription drug use in past year				
Antidiabetic drugs	33 (2.0)	29 (1.7)	55 (2.0)	55 (2.0)
Thyroid drugs	31 (1.9)	34 (2.0)	49 (1.8)	52 (1.9)
NSAIDs	339 (20.3)	351 (21.0)	563 (20.5)	570 (20.7)
Opiates	101 (6.0)	105 (6.3)	170 (6.2)	172 (6.3)
Antimigraine drugs	62 (3.7)	55 (3.3)	99 (3.6)	94 (3.4)
Antidepressants	142 (8.5)	148 (8.8)	249 (9.1)	236 (8.6)
Drugs used for peptic ulcer/gastroesophageal reflux	144 (8.6)	140 (8.4)	236 (8.6)	237 (8.6)
Pulmonary inhalants	364 (21.7)	385 (23.0)	572 (20.8)	553 (20.1)

(continued)

TABLE I. *(Continued)*

Characteristics	Matched cohort for analysis of major birth defects		Matched cohort for analysis of spontaneous abortion	
	Desloratadine users (n = 1674)	Loratadine users (n =1674)	Desloratadine users (n = 2749)	Loratadine users (n = 2749)
Leukotriene receptor antagonists	38 (2.3)	40 (2.4)	66 (2.4)	57 (2.1)
Oral corticosteroids	185 (11.1)	173 (10.3)	308 (11.2)	306 (11.1)
Topical corticosteroid groups II-IV	328 (19.6)	314 (18.8)	525 (19.1)	511 (18.6)
Nasal corticosteroids	539 (32.2)	545 (32.6)	843 (30.7)	827 (30.1)
Ophthalmological antiallergics	419 (25.0)	430 (25.7)	641 (23.3)	643 (23.4)
Other second-generation antihistamines	280 (16.7)	280 (16.7)	422 (15.4)	414 (15.1)
Drugs used for IVF in past 3 mo	106 (6.3)	115 (6.9)	141 (5.1)	139 (5.1)
No. of drugs used				
1-2	824 (49.2)	800 (47.8)	1363 (49.6)	1359 (49.4)
3-4	377 (22.5)	392 (23.4)	580 (21.1)	555 (20.2)
≥5	92 (5.5)	92 (5.5)	151 (5.5)	157 (5.7)
Hospital care utilization in past year				
No. of hospitalizations				
1	187 (11.2)	207 (12.4)	322 (11.7)	333 (12.1)
2	38 (2.3)	39 (2.3)	69 (2.5)	68 (2.5)
≥3	7 (0.4)	11 (0.7)	17 (0.6)	16 (0.6)
No. of outpatient contacts				
1	266 (15.9)	277 (16.6)	434 (15.8)	414 (15.1)
2	108 (6.5)	110 (6.6)	179 (6.5)	192 (7.0)
≥3	49 (2.9)	56 (3.4)	90 (3.3)	91 (3.3)

IVF, *In vitro* fertilization; *NA*, not available; *NE*, not estimated; *NSAID*, nonsteroidal anti-inflammatory drug.
Data are represented as n (%).

TABLE II. Association between desloratadine compared with loratadine use during pregnancy and adverse fetal safety outcomes

Outcome	Desloratadine, n (%)	Loratadine, n (%)	Measure of association (95% CI)
Primary outcomes			
Major birth defects	76 (4.5)	71 (4.2)	pOR: 1.07 (0.77-1.50)
Spontaneous abortion	256 (9.3)	230 (8.4)	HR: 1.15 (0.96-1.37)
Secondary outcomes			
Preterm birth	147 (5.6)	174 (6.6)	pOR: 0.84 (0.67-1.05)
Small size for gestational age	241 (8.9)	249 (9.2)	pOR: 0.97 (0.80-1.16)
Stillbirth	6 (0.2)	7 (0.2)	HR: 0.91 (0.31-2.70)

CI, Confidence interval; *HR*, hazard ratio; *pOR*, prevalence odds ratio.

additional comparator groups in separate cohorts and exposure definitions, which failed to show an association between desloratadine use in pregnancy and risk of major birth defects and spontaneous abortion. Of note, although we did not find an association between desloratadine and stillbirth, this analysis was based on few cases (a total of 13 cases) and hence may not be conclusive. Moreover, although our results provide reassurance by reporting no overall risk of major birth defects for pregnancies with the use of desloratadine, this study did not address the risk of specific defects. Given the relative rarity of the individual defects, the power for such analyses is limited in cohort studies.[24,25] Sufficiently powered case-control studies may provide more adequate means for such analyses.

A preplanned sensitivity analysis found a relatively small significant increase of the point estimates for induced abortion. Our *post hoc* analysis showed that the vast majority of cases of induced abortions were registered as medical abortion before 12 completed gestational weeks. This finding is not unexpected given that loratadine is a first-line recommended second-generation antihistamine during pregnancy and desloratadine is not, and as such, findings may likely reflect a higher incidence of incidental and undesired pregnancies among the desloratadine exposed group. Moreover, in Denmark, the ultrasonic malformation screening is performed between weeks 18 and 21, and importantly, results did not suggest higher rates of late induced abortions or defects among induced abortions in the pregnancies with the use of desloratadine.

The complete nationwide coverage of the registries allowed analyses of a large number of exposed pregnancies with linkage of data on an individual level facilitating a detailed characterization and independent assessment of exposure, outcome, and covariates. In addition, very few pregnancies in the desloratadine groups were excluded from the analyses because of no match in the comparative groups. Thus, this makes the results likely generalizable to similar populations. Ascertainment of prescription drug use was based on filled prescriptions and may not reflect actual use nor use on the definite date. Nonadherence to dispensed drugs would bias the results toward no effect. However, assuming women who filled their prescription at least 2 times during pregnancy were less likely to be affected by such misclassification, no statistically significant increased risk was identified among pregnancies with 2 or more

TABLE III. Sensitivity analyses of the associations between desloratadine use during pregnancy and primary outcomes

Major birth defects	No. with outcome/total no. (%)	Prevalence odds ratio (95% CI)
Cetirizine as active comparator		
Desloratadine	79/1686 (4.7%)	1.36 (0.96-1.91)
Cetirizine	59/1686 (3.5%)	1.00 (ref)
Compared with desloratadine use in last 6 mo before pregnancy only		
Desloratadine use in pregnancy	59/1257 (4.7%)	1.00 (0.69-1.45)
Desloratadine use 6 mo before pregnancy only	59/1257 (4.7%)	1.00 (ref)
No. of filled prescriptions		
Desloratadine 1 prescription	65/1458 (4.5%)	1.05 (0.74-1.49)
Desloratadine ≥2 prescriptions	11/216 (5.1%)	1.21 (0.63-2.32)
Loratadine	71/1674 (3.7%)	1.00 (ref)
Spontaneous abortion	**No. with outcome/total no. (%)**	**Hazard ratio (95% CI)**
Cetirizine as active comparator		
Desloratadine	252/2731 (9.2%)	1.04 (0.87-1.24)
Cetirizine	249/2731 (9.1%)	1.00 (ref)
Compared with desloratadine use in last 6 months before pregnancy only		
Desloratadine in pregnancy	150/1742 (8.6%)	0.84 (0.67-1.04)
Desloratadine 6 mo before pregnancy only	176/1742 (10.1%)	1.00 (ref)
No. of filled prescriptions		
Desloratadine 1 prescription	225/2286 (9.8%)	1.23 (1.02-1.47)
Desloratadine ≥2 prescriptions	31/463 (6.7%)	0.79 (0.54-1.15)
Loratadine	230/2749 (8.4%)	1.00 (ref)

CI, Confidence interval.

filled prescriptions of desloratadine, although sample sizes may have been limited in these analyses.

The primary outcomes of birth defects and spontaneous abortion have a high validity in the National Patient Registry with positive predictive values of 88% and 97%, respectively.[26,27] In a *post hoc* analysis, we examined the risk of birth defects among induced abortions and these estimates should be interpreted in view of that cases were few and that birth defects diagnosed among induced abortions have not been investigated in the Danish registries in relation to validity of these diagnoses.

A wide set of baseline characteristics were adjusted for through propensity score matching, to reduce the possibility of factors influencing the association. The included variables were well balanced across all matched cohorts and missing values were low (ranging from 0.2% to 2.6%). For the analyses of fetal death, data on smoking, parity, and multiple birth pregnancy were not obtainable. In addition, we had no information on, for example, maternal weight and folic acid use for any of the analyses. To the extent that these factors were differently distributed between study groups or not accounted for through adjustment for correlated variables (ie, proxies) included in the propensity score matching, this may have resulted in residual confounding. Sensitivity analyses with the use of additional comparative groups and exposure definitions aimed to assess the potential issue of residual confounding and confounding by indication, and did not provide evidence of significant associations to the primary outcomes.

In conclusion, this nationwide cohort study found no association between desloratadine use in pregnancy and an increased risk of adverse fetal outcomes as compared with loratadine use. Comparing desloratadine use with cetirizine use in pregnancy and with pregnancies unexposed to desloratadine but with prior use showed similar results. These results provide reassurance and may help inform clinicians, patients, and medicinal regulatory agencies regarding the fetal safety of desloratadine.

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