Pregnancy outcome after gestational exposure to loratadine or antihistamines: A prospective controlled cohort study

Orna Diav-Citrin, MD,[a] Svetlana Shechtman, PhD,[a] Alona Aharonovich, BSc,[b]* Larisa Moerman, MD,[a] Judy Arnon, PhD,[a] Rebecka Wajnberg, MSc,[a] and Asher Ornoy, MD[a,b] *Jerusalem, Israel*

Background: Loratadine is a second-generation histamine H_1-receptor antagonist, used in the treatment of allergic conditions. No prospective controlled trials on loratadine in human pregnancy have been published to date.
Objective: To determine whether the use of loratadine or other antihistamines (OAH) is associated with an increased risk of major anomalies.
Methods: Callers who were counseled by the Israeli Teratogen Information Service in regard to loratadine or OAH exposure during pregnancy were prospectively collected and followed up. Pregnancy outcome was compared among three exposure groups: loratadine, OAH, and a control group of patients who were counseled for nonteratogenic exposure, nonteratogenic controls (NTC). The OAH included astemizole, chlorpheniramine, terfenadine, hydroxyzine, promethazine, and dimetindene.
Results: We followed up 210 pregnancies exposed to loratadine (77.9% in the first trimester) and 267 pregnancies exposed to OAH (64.6% in the first trimester) and compared pregnancy outcome with that of 929 NTC. The rate of congenital anomalies did not differ among the groups [loratadine: 4/175 (2.3%), OAH: 10/247 (4.0%), NTC: 25/844 (3.0%), *P* = .553, relative risk (RR), 0.77; 95% confidence interval (CI), 0.27 to 2.19, (loratadine vs NTC); RR, 0.56; 95% CI, 0.18 to 1.77, (loratadine vs OAH)]. The rate did not differ between those exposed to antihistamines in the first trimester and the control patients [loratadine: 1/126 (0.8%), OAH: 7/146 (4.8%), NTC: 25/844 (3.0%), *P* = .152, RR, 0.27; 95% CI, 0.04 to 1.94, (loratadine vs NTC); RR, 0.17; 95% CI, 0.02 to 1.33, (loratadine vs OAH)].
Conclusions: This study on the use of loratadine in human pregnancy suggests that this agent does not represent a major teratogenic risk. The study was powered to find a 3-fold increase in the overall rate of major anomalies. (J Allergy Clin Immunol 2003;111:1239-43.)

Key words: *Loratadine, antihistamines, pregnancy outcome, major anomalies*

Abbreviations used
NTC: Nonteratogenic control subjects
OAH: Other antihistamines
TIS: Teratogen Information Service

Loratadine is a long-acting, second-generation histamine H_1-receptor antagonist with minimal sedative effects when given at the recommended dose. It is used for the symptomatic relief of various allergic conditions including rhinitis and chronic urticaria. Allergic conditions are common in women of reproductive age with allergic rhinitis, affecting approximately one third. Teratogenicity studies in rats and rabbits performed by the manufacturer were negative with oral doses up to 75 and 150 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis.[1] No prospective controlled trials on loratadine in human pregnancy have been published to date. In one prospective series, no congenital anomalies were observed among 16 infants whose mothers were treated with loratadine during the first trimester of pregnancy.[2] Contrary to the above, a recent study raised concern for an increased risk for hypospadias after gestational exposure to loratadine.[3] Fifteen cases of hypospadias were found among 2780 children of women who had taken loratadine during pregnancy in the Swedish Birth Registry (5.6 expected). The majority had mild glandular hypospadias, and one had a penile hypospadias. Among 5116 infants exposed to other antiallergic drugs, only 6 had hypospadias (10.2 expected).

The same registry was recently used to identify 17,776 pregnancies in which various antihistamines were reported to be used in early pregnancy with no teratogenic effect.[4] Chlorpheniramine and hydroxyzine are first-generation antihistamines for which there is extensive literature on their safe use in pregnancy.[5-8] First-generation antihistamines are generally preferred over their second-generation counterparts, based on their longer duration in clinical use, leading to more conclusive evidence on safety in pregnancy. Astemizole and terfenadine are second-generation antihistamines, which were removed from the market in the United States because of potential cardiac toxicity. There are studies on their safe use in pregnancy.[6,9,10]

The aim of our study was to prospectively evaluate the rate of major anomalies after exposure to loratadine during pregnancy. This rate was compared with the one

From the [a]Israeli Teratogen Information Service, Israel Ministry of Health, and the [b]Hebrew University Hadassah Medical School, Jerusalem, Israel.
Supported in part by Schering-Plough.
*Served as partial fulfillment of the requirements for the Master degree in Clinical Pharmacy of the Hebrew University.
Received for publication December 11, 2002; revised February 18, 2003; accepted for publication February 26, 2003.
Reprint requests: Prof Asher Ornoy, The Israeli Teratogen Information Service, Laboratory of Teratology, The Hebrew University–Hadassah Medical School and Israel Ministry of Health, PO Box 12272, Jerusalem 91120, Israel.
© 2003 Mosby, Inc. All rights reserved.
0091-6749/2003 $30.00 + 0
doi:10.1067/mai.2003.1499

TABLE I. Distribution of agents in the OAH group

Antihistamine	n (%)
Astemizole	81 (30.3)
Chlorpheniramine	68 (25.5)
Terfenadine	40 (15.0)
Hydroxyzine	37 (13.9)
Promethazine	22 (8.2)
Dimetindene	19 (7.1)

TABLE II. Trimester of exposure in the loratadine and OAH groups

	Loratadine	OAH
First trimester at least (throughout pregnancy)	77.9% (2.0%)	64.6% (4.3%)
Second trimester	11.8%	21.0%
Third trimester	10.3%	14.4%

found in two groups. The first consisted of women who were counseled for pregnancy exposure to other antihistamines (OAH) for which there is extensive literature on their safe use in pregnancy. The second group, nonteratogenic control subjects (NTC), consisted of pregnant women exposed to nonteratogenic agents who contacted the Israeli Teratogen Information Service (TIS).

METHODS

This prospective cohort included all pregnant women who contacted the Israeli TIS (directly or through their health care providers) between 1995 and 2001 for information about gestational exposure to loratadine. The loratadine-exposed group was compared with two groups. The first group (OAH) consisted of pregnant women who sought counseling at the Israeli TIS between 1990 and 2001 after exposure to the following antihistamines: astemizole, chlorpheniramine, terfenadine, hydroxyzine, promethazine, and dimetindene. The second group (NTC) consisted of women who had been counseled during pregnancy in regard to exposures not known to be teratogenic in a similar time frame. Part of this control group has previously been used.[11,12] The criteria for selection of the NTC group have been previously described.[12] We aimed at a 1:1 ratio between the loratadine and OAH groups. To increase the power of our study, we tried to reach a 1:4 ratio between the exposed (loratadine and OAH) and NTC groups.

Details of exposure were collected during pregnancy and before pregnancy outcome was known, through the use of a structured questionnaire. Standardized data collection forms were used to record the following information by telephone: maternal demographics, medical and obstetric history, exposure details (dose, duration, timing in pregnancy), and concurrent exposures. After the expected date of delivery, follow-up was conducted by a telephone interview with the woman, with the use of a structured questionnaire to obtain details on the pregnancy outcome, gestational age at delivery, birth weight, and congenital anomalies. This offspring follow-up was performed between the neonatal period and 6 years of age. However, in most cases, it was carried out within the first year of life.

The primary outcome of interest was the rate of major anomalies; that is, those having a structural abnormality that has serious medical, surgical, or cosmetic consequences.[13] In the case of multiple births, each live-born infant was included in the analysis. Secondary end points were the rates of live birth, miscarriage, pregnancy termination, stillbirth, and ectopic pregnancy; the rate of premature births (≤37 weeks); gestational age at delivery; and birth weight. Gestational age in the current study applies to weeks after the last menstrual period.

Statistical analysis

Categoric data were compared by χ^2 test or Fisher exact test. Continuous data did not follow normal distribution and were compared by means of the Kruskal-Wallis test (for 3 groups) or Mann-Whitney test (for 2 groups). The data are expressed as ratios or percentages for categoric data. Continuous data are presented through the use of medians with interquartile ranges. For pairwise comparisons, the Bonferroni method was applied. Relative risk and power calculation were performed with Epi Info 2000 software. Logistic regression analysis was used to evaluate the relative contribution of various predictors to the differences in miscarriage rate.

RESULTS

We prospectively collected and followed up data on 210 pregnancies exposed to loratadine and 267 pregnancies exposed to other antihistamines. In the loratadine group, 203 (96.7%) took loratadine, whereas 7 (3.3%) took it in a preparation that contains a combination of 5 mg loratadine and 120 mg pseudoephedrine as Clarinase. The median daily dose of loratadine was 10 mg (10 to 10), for a median duration of 8 days (4 to 14). The distribution of agents in the OAH group is presented in Table I. The median duration of treatment in the OAH group was 7 days (5 to 19). The timing of exposure in pregnancy in the loratadine and OAH groups according to trimesters is presented in Table II. The indication for treatment in the loratadine group, based on the caller's report was allergy in 74 (35.1%), respiratory conditions in 42 (19.9%), skin conditions in 25 (11.8%), and in 70 (33.2%) the indication was not specified. The indication for treatment in the OAH group, based on the caller's report, was allergy in 70 (25.5%), skin conditions in 49 (17.9%), respiratory conditions in 39 (14.2%), hyperemesis gravidarum in 1 (0.4%), and in 115 (42.0%) the indication was not specified. At least 1 additional antihistamine was reported in 49 pregnancies (23.3%) of the loratadine group and 50 (18.7%) of the OAH group. Additional other exposures (ie, antibiotics, corticosteroids, nasal sympathomimetics, inhaled β_2-agonists, antipyretics) were reported in 137 (65.2%) of the pregnancies in the loratadine group and 179 (67.0%) in the OAH group.

Our follow-up rate was 73.6% in the loratadine group, 50.2% in the OAH group, and 25.1% in the NTC group.

Maternal characteristics

A comparison of maternal characteristics among the three groups is presented in Table III. The women in the loratadine group called at a significantly earlier median gestational age compared with the women in the OAH and control groups [8.0 weeks (loratadine), 10.0 (OAH), 10.0 (NTC); $P = .002$]. The women in the loratadine group were older compared with those in the OAH and control groups [median maternal age, 31.5 years (loratadine), 30.0 (OAH), 30.0 (NTC); $P = .005$]. No significant differences were found between the three groups regarding obstetric history.

TABLE III. Maternal characteristics

	Loratadine (n = 210)	OAH (n = 267)	Control (n = 929)	*P* value
Median GA at call (wk) (interquartile range)	8.0*† (6.0-14.0)	10.0 (7.0-20.5)	10.0 (7.0-18.0)	.002
Median age (y) (interquartile range)	31.5*† (28.0-35.0)	30.0 (26.0-34.0)	30.0 (26.0-34.0)	.005
Gravidity (%)	n = 203	n = 245	n = 891	
G1	42 (20.7)	57 (23.3)	218 (24.5)	.513
G2-6	152 (74.9)	178 (72.7)	625 (70.1)	.355
≥G7	9 (4.4)	10 (4.1)	48 (5.4)	.653
Parity (%)	n = 201	n = 221	n = 890	
P0	47 (23.4)	73 (33.0)	257 (28.9)	.090
P1-4	148 (73.6)	139 (62.9)	590 (66.3)	.054
≥P5	6 (3.0)	9 (4.1)	43 (4.8)	.497
Miscarriages (%)	n = 198	n = 238	n = 876	
None	158 (79.8)	185 (77.7)	708 (80.8)	.567
One	28 (14.1)	38 (16.0)	116 (13.2)	.555
Two or more	12 (6.1)	15 (6.3)	52 (5.9)	.978

OAH, Other antihistamines; *GA,* gestational age; *G,* gravidity; *P,* parity.
*Significant difference in comparison with OAH group.
†Significant difference in comparison with control group.

TABLE IV. Pregnancy outcome in the loratadine, OAH, and control groups

Pregnancy outcome	Loratadine (n = 210)	OAH (n = 268)	Control (n = 929)	*P* value
Deliveries of live-born infants (%)	174 (82.9)	239 (89.2)	819 (88.2)	.074
Miscarriages (%)	24 (11.4)†	13 (4.9)	67 (7.2)	.023
ETOP (%)	12 (5.7)	14 (5.2)	37 (4.0)	.442
Ectopic pregnancies (%)	0	0	1 (0.1)	.773
Stillbirths (%)	0	2 (0.7)	5 (0.5)	.493
Major anomalies (%)‡§	4/175 (2.3)	10/247 (4.0)	25/844 (3.0)	.553
Major anomalies (%)‡§ of AH exposed in T1	1/126 (0.8)	7/146 (4.8)	25/844 (3.0)	.152
Median GA (wk) (interquartile range)	40.0 (39.0-41.0)	40.0 (39.0-41.0)	40.0 (38.0-41.0)	.129
Preterm deliveries (%)				
≤37 wk	11/170 (6.5)	19/229 (8.3)	90/796 (11.3)	.101
Median birth weight§ (g) (interquartile range)	3275 (3000-3548)	3245 (2883-3500)	3280 (2930-3600)	.302

OAH, Other antihistamines; *ETOP,* elective termination of pregnancy; *AH,* antihistamines; *T1,* first trimester; *GA,* gestational age.
*One twin pregnancy considered twice because one was reduced because of prenatal diagnosis of Down syndrome whereas the other carried to delivery.
†Significant difference in comparison with OAH group.
‡Including 1 stillbirth diagnosed with anomalies and 1 ETOP due to prenatally diagnosed anomalies in the OAH group and 9 in the control group.
§Including multifetal pregnancies.

Pregnancy outcome

A comparison of pregnancy outcome among the three groups is presented in Table IV. There was no increase in the rate of major anomalies reported in the loratadine group compared with the OAH and control groups [loratadine: 4/175 (2.3%), OAH: 10/247 (4.0%); NTC: 25/844 (3.0%); $P = .553$, relative risk (RR), 0.77; 95% confidence interval (CI), 0.27 to 2.19, (loratadine vs NTC); RR, 0.56; 95% CI, 0.18 to 1.77, (loratadine vs OAH)]. This comparison includes major congenital anomalies among live-born infants, elective terminations of pregnancy due to prenatally diagnosed anomalies (none in the loratadine group, 1 in the OAH group, and 9 in the control group), and stillbirths with anomalies (1 in the OAH group). A similar comparison was repeated when the analysis included pregnancies exposed to loratadine or OAH in the first trimester only, and there was no increase in the rate of congenital anomalies among the three groups [loratadine: 1/126 (0.8%), OAH: 7/146 (4.8%), NTC: 25/844 (3.0%); $P = .152$; RR, 0.27; 95% CI, 0.04 to 1.94, (loratadine vs NTC); RR, 0.17 95% CI, 0.02 to 1.33, (loratadine vs OAH)].

In the loratadine group there was one set of twins; in the OAH group, 7 sets of twins; and in the control group, 15 sets of twins and 1 set of triplets. Live-born infants include those who resulted from multifetal pregnancies. They are independently included in the analysis of major anomalies and in the analysis of birth weight. One pregnancy is considered twice, as one was reduced because of prenatal diagnosis of Down syndrome, whereas the other was carried to delivery.

A significantly higher rate of miscarriages was found in the loratadine group (Table IV). To evaluate the relative contribution of various predictors to the differences in miscarriage rate, logistic regression was performed. Type of exposure (loratadine, OAH, and NTC), history of miscarriages, maternal age, and gestational age at call were entered to the model. The only significant predictors were maternal age [$P < .001$, Wald = 13.494, Exp(B) = 0.924] and gestational age at call [$P < .001$, Wald = 27.354,

TABLE V. Rate of major anomalies in the OAH group according to drug

Drug	Entire OAH group	First trimester
Astemizole	4/73 (5.5%)	3/50 (6.0%)
Chlorpheniramine	1/63 (1.6%)	0/23 (0%)
Terfenadine	2/35 (5.7%)	2/27 (7.4%)
Hydroxyzine	1/33 (3.0%)	1/20 (5.0%)
Promethazine	2/23 (8.7%)	1/13 (7.7%)
Dimetindene	0/20 (0%)	0/13 (0%)

TABLE VI. Major congenital anomalies in the loratadine and OAH groups

Group	Type of anomaly	Details of exposure	Additional exposures	Follow-up/comments
Loratadine	Tourette syndrome	First trimester	Phenytoin, carbamazepine, ciprofloxacin	
Loratadine	Facial hemangiomas	Wk 16	None	Steroid treatment age 3-8 mo, sclerosant injection, laser therapy, surgical interventions
Loratadine	VSD Undescended testes	Wk 27	Codeine, ranitidine	VSD - improving on echocardiography Surgical correction
Loratadine	VSD	Wk 31	Topical betamethasone	
OAH	CDH	Astemizole, wk 3	Dental radiography, rubella vaccine, topical triamcinolone, nystatin, neomycin, gramicidin,	
OAH	Genetic problem	Astemizole, wk 22	None	Positive family history
OAH	Urinary tract anomaly, duplication of right collecting system	Astemizole, first trimester	Topical fluocortolone, betamethasone, permethrin	
OAH	ASD, large VSD + multiple small VSDs	Astemizole, wk 12	Amoxicillin, Pseudoephedrine, nasal oxymetazoline	CHF, digoxin and diuretics treatment, surgery at 2 mo of age
OAH	CDH	Chlorpheniramine, wk 28	Topical betamethasone	Casting
OAH	Right kidney aplasia, short right femur and tibia	Hydroxyzine, wk 2	None	Stillbirth
OAH	Cleft lip	Promethazine	Roxithromycin	Surgical correction
OAH	Down syndrome	Promethazine, First trimester	None	ETOP
OAH	Bilateral inguinal hernia	Terfenadine, wk 5	None	Surgical correction at age 1 mo
OAH	CDH	Terfenadine, wk 3	None	Braces/harness for 7 mo

OAH, Other antihistamines; *VSD*, ventricular septal defect; *CDH,* congenital hip dysplasia; *ASD,* atrial septal defect; *CHF,* congestive heart failure; *ETOP,* elective termination of pregnancy.

Exp(B) = 1.147]. There were no significant differences among the three groups in the rate of deliveries of live-born infants, ectopic pregnancies, stillbirths, and preterm deliveries. No significant differences were found in the median gestational age at delivery or in birth weight.

Table V lists the rate of congenital anomalies in the OAH group according to the different drugs and time of exposure. No significant differences were observed when the rate of anomalies in the NTC group was compared with those in the various other antihistamine drugs.

The reported major anomalies in the loratadine and OAH groups are listed in Table VI. There was no specific pattern of anomalies in the offspring of women in both groups. Several anomalies were not considered major anomalies in the 3 groups, that is, cardiac murmur without echocardiographic confirmation of a cardiac defect, patent ductus arteriosus in a preterm infant, suspected hydronephrosis that later resolved or with a normal kidney scan, hemangiomas that did not require medical or surgical intervention.

DISCUSSION

This prospective cohort study followed up 210 pregnancies to examine the rate of major anomalies after exposure to loratadine, 267 pregnancies exposed to OAH, and 929 NTC. The malformation rates in the three groups were within the expected baseline risk for the general population. No specific pattern of anomalies was found in the loratadine- or OAH-exposed groups, supporting lack of a teratogenic effect. None of the described defects is plausibly explained by the exposure to loratadine in pregnancy. Källén and Otterblad Olausson[3] raise concern about a possible increased risk (<1%) for hypospadias after in utero loratadine exposure, despite lack of biological plausibility.

In the current study, no case of hypospadias was reported among the loratadine-exposed infants. We looked for the prevalence of hypospadias at our TIS database among the pregnancies with completed follow-up. There were 6 reported cases of hypospadias among 3908 live-born infants with known outcome. Assuming that half of the offspring are males, the prevalence rate is 1 in 325 male infants. Our numbers in the loratadine-exposed group are insufficient to properly address the question of an increased risk for hypospadias in infants exposed in utero to loratadine. However, we wonder about the possible causal relation between glandular hypospadias and early in utero loratadine exposure in the study published by Källén and Otterblad Olausson[3] in regard to timing of exposure and intrauterine development. Drug utilization information was collected and recorded at 10 to 12 weeks after the last menstrual period (8 to 10 weeks after conception) and refers to the first trimester of pregnancy.[3] The distal part of the urethra in the male is derived from the glandular plate and meets with the spongy urethra at 12 weeks after conception.[14] The most distal portion of the urethra is formed during the fourth month of pregnancy, when ectodermal cells from the tip of the glans invaginate to form the external urethral meatus.[15] The mean elimination half-lives for loratadine and its major metabolite, descarboethoxyloratadine, are 8.4 and 28 hours, respectively.[16] As the majority of cases in the study published by Källén and Otterblad Olausson[3] had mild glandular hypospadias, early first trimester exposure does not plausibly explain them, unless the drug was continued beyond 10 to 12 weeks after the last menstrual period.

A sample size of 175 live births in the loratadine-exposed group with a ratio of 1:4.8 to the control group, power of 80%, assuming a baseline risk of 3% for major anomalies, enables detection of a 2.78-fold increase in the rate of major anomalies (with 95% CI). A sample size of 129 live births exposed in the first trimester with a ratio of 1:6.5 to the control group, with similar assumptions, enables detection of a 3.07-fold increase in the rate of major anomalies. The study is not powered to find a smaller increase in the overall rate of major anomalies.

There was a significantly higher miscarriage rate in the loratadine group in comparison to the OAH group (Table IV). Higher miscarriage rate may be associated with an earlier gestational age at call, as most miscarriages occur during the first 3 months of pregnancy. As shown in Table III, the median gestational age at call was significantly lower in the loratadine group compared with both the OAH and NTC groups. The risk of miscarriages also increases with maternal age. Indeed, the logistic regression demonstrated that the risk of miscarriages was higher with an earlier gestational age at call and advanced maternal age. Loratadine exposure did not have a significant predictive effect on the rate of miscarriages. Similarly, history of miscarriages did not contribute to the observed difference.

The safety of loratadine in pregnancy is difficult to investigate in a randomized, controlled manner because of ethical considerations. The current prospective controlled cohort study, despite its limitations (ie, reliance on self-reported drug exposure and maternal interview as a source for outcome data), is a valid approach to the question. The same procedure, applied to the three arms of the study, minimizes the potential biases.

The current study, which is the first prospective, controlled study on the use of loratadine in pregnancy, suggests that this agent does not represent a major teratogenic risk. The study is powered to find a 3-fold increase in the overall rate of major anomalies. The use of OAH, as in most previous studies, was not associated with an increased risk for major anomalies. However, because this study is still relatively small and could not properly address the potential risk for hypospadias, continuing long-term surveillance of pregnancy outcome is needed.

REFERENCES

1. Product Information. Claritin. Schering Corporation, 2001.
2. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol 1998;105:882-9.
3. Källén B, Otterblad Olausson P. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? Int J Risk Safety Med 2001;14:115-9.
4. Källén B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002;11:146-52.
5. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton, Mass: Publishing Sciences Group; 1977.
6. Schatz M, Petitti D. Antihistamines and pregnancy. Ann Allergy Asthma Immunol 1997;78:157-9.
7. Erez S, Schifrin BS, Dirim O. Double-blind evaluation of hydroxyzine as an antiemetic in pregnancy. J Reprod Med 1971;7:35-7.
8. Einarson A, Bailey B, Jung G, Spizziri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997;78:183-6.
9. Pastuszak A, Schick B, D'Alimonte D, Donnenfeld A, Koren G. The safety of astemizole in pregnancy. J Allergy Clin Immunol 1996;98:748-50.
10. Loebstein R, Lalkin A, Addis A, Costa A, Lalkin I, Bonati M, et al. Pregnancy outcome after gestational exposure to terfenadine: a multicenter, prospective controlled study. J Allergy Clin Immunol 1999;104:953-6.
11. Ornoy A, Arnon J, Moerman L, Shechtman S, Lukashova I. Is benzodiazepine use during pregnancy really teratogenic? Reprod Toxicol 1998;5:511-5.
12. Diav-Citrin O, Shechtman S, Gotteiner T, Arnon J, Ornoy A. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001;63:186-92.
13. Holmes LB. Need for inclusion and exclusion criteria for the structural abnormalities recorded in children born from exposed pregnancies. Teratology 1999;59:1-2.
14. Moore KL. The developing human: clinically oriented embryology. 4th edition. Philadelphia, Pa; WB Saunders Company; 1988.
15. Sadler TW. Langman's medical embryology. 7th edition. Baltimore, Md; Williams & Wilkins; 1996.
16. Parfitt K, Martindale. The complete drug reference. 32nd edition. Taunton, Mass: Pharmaceutical Press; 1999.

ADDENDUM

After the acceptance of the current article, another study by Moretti et al on the safety of loratadine was published: Moretti ME, Caprara D, Coutinho CJ, Bar-Oz B, Berkovitch M, Addis A, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. J Allergy Clin Immunol 2003;111:479-83.