

Pregnancy outcome after gestational exposure to terfenadine: A multicenter, prospective controlled study

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Background: Terfenadine is a selective, nonsedative, H₁-blocker antihistamine used for a variety of allergic conditions. The widespread popularity of terfenadine and its use by many women in their reproductive age raises concerns regarding its safety during pregnancy. Presently, no prospective controlled study has addressed its safety during gestation.

Objective: We sought to determine whether terfenadine use during pregnancy is associated with an increased risk of major malformations, decreased birth weight, perinatal complications, or developmental delays.

Methods: A multicenter, prospective controlled study was performed. Pregnant women exposed to terfenadine during gestation were matched with control subjects exposed to drugs not known to adversely affect pregnancy outcome. The primary end point was the incidence of major malformations. Secondary outcomes of interest were pregnancy outcome, rates of preterm delivery, birth weight, and developmental milestones. **Results:** One hundred eighteen women were exposed to terfenadine during pregnancy. Among those exposed during the first trimester ($n = 65$), rates of major malformations in the terfenadine group did not differ from rates in their matched control subjects (0% vs 2%; relative risk, 0.57; 95% confidence interval, 0.06-5.39; $P = .53$). The birth weight in the terfenadine-exposed newborns was significantly lower compared with that in their matched control subjects (3335 ± 582 vs 3499 ± 617 g; $P = .04$). However, the rates of birth weight below 2500 g and birth weight below the 10th percentile for gestational age were not different between the groups. Univariate and multiple regression analysis revealed that none of the terfenadine therapy-related factors (daily dose, duration of therapy, and trimester of exposure) had a significant predictive effect on birth weight. Gestational age at delivery, rates of preterm deliveries, and developmental milestones were comparable between the groups.

Conclusions: On the basis of the limited sample size of this study, it appears that terfenadine is not associated with a 6-fold or greater increased incidence of major malformations. Terfenadine use during gestation was not associated with increased rates of prematurity or developmental delays. Further studies will be needed to confirm the finding of lower

birth weight in newborns exposed to terfenadine. (*J Allergy Clin Immunol* 1999;104:953-6.)

Key words: Terfenadine, pregnancy outcome, malformations

It is estimated that allergic diseases occur in approximately 20% to 30% of women of childbearing age, making these diseases a common group of medical conditions that might complicate pregnancy.^{1,2} Antihistamines are used for chronic urticaria, seasonal and perennial allergic rhinitis, conjunctivitis, and other allergic conditions.³ In light of the widespread use of the nonsedating selective H₁-antagonists, there is a potential for substantial use of these agents by women of childbearing age (ie, pregnant women). However, because human reproductive data are scarce, their use during pregnancy cannot be recommended. Because of these concerns and because antihistamines were shown to cross the placenta,^{4,5} there is a clear need to evaluate their fetal safety. Moreover, because almost half of all pregnancies are unplanned,⁶ women of the reproductive age group may inadvertently expose their fetuses to terfenadine.

Terfenadine, a butyrophenone-derivative antihistamine, is still available in Canada, whereas its metabolite fexofenadine has replaced its use in the United States mainly because of interaction between terfenadine and other drugs, which resulted in fatal cardiac toxicity.^{7,8} The widespread use of terfenadine as an antihistamine emerged because unlike the first-generation H₁-receptor antagonists, it does not cause the typical central nervous system sedation, drowsiness, and alterations of mood or memory. Moreover, terfenadine does not potentiate the impairment of psychomotor skills caused by alcohol or benzodiazepines.⁹

Animal reproductive studies have demonstrated that oral terfenadine doses up to 63-fold the human recommended daily dose did not cause structural birth defects. However, reproduction studies in rats have revealed decreased pup weight gain and survival together with maternal toxicity, as shown by reduced implants and higher postimplantation losses. This was observed when terfenadine was administered throughout pregnancy and lactation at an oral dose of $300 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, which is approximately 20 times the maximum recommended human daily dose on a milligram per square meter basis.¹⁰ Postmarketing surveillance conducted by the manufacturer found no cluster or pattern of malformations to suggest association between terfenadine use dur-

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Received for publication May 14, 1998; revised July 14, 1999; accepted for publication July 26, 1999.

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0091-6749/99 \$8.00 + 0 1/1/101790

TABLE I. Characteristics of mothers exposed to terfenadine during pregnancy compared with those of control subjects

Characteristics	Terfenadine group (n = 118)	Control subjects (n = 118)	P value
Maternal age (y)	31.7 ± 4.3	31.5 ± 4.3	.7
Gravidity			
1	46/118	45/118	1.0
2	35/118	35/118	.8
3	18/118	20/118	.8
≥4	19/118	18/118	1.0
Parity			
0	53/118	54/118	1.0
1	40/118	42/118	.9
2	17/118	15/118	.8
≥3	8/118	7/118	1.0
Previous miscarriages			
0	94/118	92/118	.9
1	18/118	21/118	.7
≥2	6/118	5/118	1.0
Previous elective abortions			
0	111/118	108/118	.6
1	5/118	9/118	.4
2	2/118	1/118	1.0
Alcohol use (%)			
None	80	81	.9
Light	20	19	.9
Smoking (%)			
None	90.4	89.6	.9
Light	9.6	10.4	.9

Light alcohol consumption is defined as less than 15 g of absolute alcohol per day. Light cigarette smoking is defined as less than 5 cigarettes per day.

ing pregnancy and congenital malformations (Hoescht Marion Roussel Canada, Inc, personal communication 1998). The Michigan Medicaid Survey did not find an increased incidence of major malformations in 1034 women exposed to terfenadine compared with nonexposed control subjects.¹¹ These findings were further supported by a preliminary report by Schick et al.¹² However, prospective controlled human studies are lacking.

Faced with insufficient data on the fetal safety of terfenadine, pregnant women often contact a Teratology Information Service¹³ for counseling regarding the risk of gestational exposures to this drug. This has led us to realize that the drug is widely used by women and that fetal safety data are urgently needed. We report here on the first prospective, controlled multicenter study of pregnancy outcome after terfenadine use during pregnancy.

METHODS

We enrolled all women exposed to terfenadine who called one of the 2 participating Teratogen Information Services: Motherisk (Toronto, Canada) and Centro Regionale d'Informazione sul Farmaco (Milan, Italy). The methodology of data collection and follow-up were consistent between the centers by making use of a structured questionnaire. Data were collected at the time of exposure and before pregnancy outcome was known and included maternal age, gravity, parity, the number of spontaneous and therapeutic

abortions, smoking and alcohol consumption habits, the indication for therapy, daily dose of terfenadine, duration of its use, trimester of exposure, and maternal and genetic history.

All women and their family physicians were called after the expected delivery date for a follow-up telephone interview that confirmed the information ascertained from the first interview and collected information regarding the outcome of pregnancy, birth weight, physical findings, any birth defect, and developmental milestones achievement according to the Denver Developmental Scale.

Although maternal reports of developmental milestones have not been specifically validated, these reports are considered reliable on the basis of data that shows a high correlation between maternal reports and medical records for pregnancy-related outcomes, such as birth weight and gestational age.¹⁴ Maternal reports of all major malformations, gestational age at delivery, birth weight, perinatal complications (eg, emergency cesarean delivery, forceps or vacuum delivery, or the need for neonatal intensive care unit) were confirmed by their family physicians in writing on the basis of medical records review.

Each woman exposed to terfenadine during gestation was subsequently matched to control subjects selected from the Motherisk database. For control subjects, we recruited women who were counseled at Motherisk regarding the use of drugs not known to adversely affect pregnancy outcome (eg, dental radiography and acetaminophen). Control subjects were matched for maternal age (± 2 years), smoking, and alcohol consumption habits. Light alcohol consumption was defined as daily consumption of up to 15 g of absolute alcohol (150 mL of wine or 1 bottle of regular beer). Heavy alcohol consumption was defined as consumption of greater than 30 g of absolute alcohol per day. All our patients were either not alcohol drinkers or light alcohol drinkers. Light cigarette smoking was defined as smoking up to 5 cigarettes a day, and heavy cigarette smoking was defined as smoking more than 5 cigarettes a day.

Our primary outcome of interest was the rate of major malformations, as defined by Marden et al.¹⁵ Secondary outcomes of interest were rates of live births, therapeutic abortions, fetal deaths, gestational age at delivery, birth weight, and developmental milestones.

Each of the participating centers received institutional ethics approval.

Data for the 2 groups are presented as means ± SDs and proportions as appropriate. Continuous data between patients and control subjects were compared by using the Student *t* test and the Mann-Whitney rank-sum test as appropriate. Categorical data were compared by χ^2 analysis. The rates of major malformations, therapeutic abortions, and stillbirths were analyzed by using the Fisher exact test. Relative risks and 95% confidence intervals were also calculated. Bivariate correlation coefficients were computed by using the Pearson test to examine the potential relationship between birth weight and terfenadine daily dose, duration of terfenadine treatment, and trimester of exposure. Finally, multiple linear regression analysis was used to study the effects of concurrent steroid treatment and the presence of maternal asthma on birth weight.

RESULTS

Data for a total of 118 women exposed to terfenadine during pregnancy were collected. One hundred two (86%) of the women were from Toronto (Motherisk), and 16 (14%) were from Milan (Centro Regionale d'Informazione sul Farmaco). To exclude the possibility of selection bias, maternal characteristics were compared by using a cross-center analysis: maternal age, gravity, parity, the number of previous spontaneous and therapeutic abortions, alcohol, and smoking habits were not

TABLE II. Pregnancy outcome for women exposed to terfenadine during pregnancy compared with that of control subjects

Outcome or characteristic	Terfenadine group (n = 118)		Control subjects (n = 118)		Relative risk (95% confidence interval)	P value
	No.	%	No.	%		
Live births	111/118	94	112/118	95	0.99 (0.93-1.05)	1.0
Therapeutic abortion	1/118	1	2/118	2	0.50 (0.05-5.4)	1.0
Stillbirth	2/118	2	0/118	0	2.02 (1.77-2.30)	.49
Major malformations per live birth (exposure first trimester only)	0/65	0	2/111	2	0.57 (0.06-5.39)	.53
Gestational age (wk)	39.5 ± 2.1		39.2 ± 1.9	—		.31
Preterm (<37 wk)	9/111	81	8/98	82	1.00 (0.33-2.97)	.81
Cesarean delivery	18/112	16	18/112	16	1.00 (0.55-1.82)	.85
Perinatal complications*	20/110	18	11/90	12	1.21 (0.90-1.63)	.33
Birth weight (g)	3335 ± 582		3499 ± 617	—		.04
Birth weight <2500 g	8/111		6/112		1.16 (0.72-1.86)	.76
<10th percentile birth weight for gestational age	5/111		2/112		1.46 (0.89-2.37)	.43
Weight gain (kg)	14.2 ± 4.7		14.7 ± 5.5	—		.46

*Emergency cesarean delivery, forceps or vacuum delivery, or the need for neonatal intensive care unit.

statistically different among the women at the 2 centers.

Exposure during organogenesis was reported by 65 (55%) women, whereas the rest used terfenadine later in pregnancy. The mean daily dose ranged from 30 mg to 120 mg. The most common condition for which terfenadine was used during gestation was seasonal allergic rhinitis (82 women, 69%) followed by urticaria (7 women, 6%), animal or food allergies (5 women, 4%), common cold (4 women, 3%), and sinus infections (4 women, 3%). For 15 women the indication for terfenadine therapy was not clear.

Twenty-five (21%) women used other H₁-antagonists or decongestants in addition to terfenadine; 16 (14%) women used inhaled H₁-agonists, and 13 (11%) women used either inhaled or oral corticosteroids.

Maternal characteristics

Maternal characteristics are shown in Table I. The terfenadine and control groups were of similar ages. Rates of light alcohol consumption did not differ between the study and control groups (20% vs 19%; *P* = .9). No cases of heavy alcohol consumption were reported in the study or control groups. Similarly, light cigarette smoking was not different between the groups (9.6% vs 10.4%; *P* = .9). No cases of heavy smokers were reported.

Pregnancy outcome

Pregnancy outcomes are shown in Table II. We found no differences in the rates of major malformations between children exposed to terfenadine during organogenesis and children of mothers in the control group (0 of 65 vs 2 of 111, *P* = .53). Birth weight was significantly lower among the terfenadine-exposed women (3338 ± 582 g vs 3499 ± 617 g among the women in the control group (*P* = .04).

However, by using linear regression analysis, we

TABLE III. Acquisition of milestones as defined by the Denver Developmental Scale

Milestones	Age acquired (mo)		P value
	Terfenadine group	Control group	
Smiling (n = 78)	1.6 ± 0.5	1.4 ± 0.6	.16*
Lifting (n = 73)	2.2 ± 0.9	2.3 ± 1.1	.68*
Sitting (n = 58)	6.0 ± 1.0	5.8 ± 1.2	.24*
Crawling (n = 46)	7.7 ± 1.4	7.2 ± 1.4	.40*
Walking (n = 55)	11.7 ± 2.6	11.9 ± 2.5	.78*

n, No. of matched pairs.

*As determined by using the Student *t* test.

found no statistically significant correlation between birth weight and the daily terfenadine dose (*r* = 0.004, *P* = .97), birth weight and the duration of terfenadine treatment (*r* = 0.062, *P* = .58), and birth weight and trimester of exposure to terfenadine (*r* = 0.046, *P* = .68). Moreover, all the other potential predictors, such as concurrent use of steroids and the presence of maternal asthma analyzed by multiple regression analysis, had no statistically significant predictive value on birth weight. The 2 groups did not differ in weight gain and gestational age at delivery. Similarly, rates of birth weight below 2500 g and less than the 10th percentile for gestational age were comparable between the groups. Developmental milestone achievements did not differ between the children of the mothers in the 2 groups (Table III).

DISCUSSION

It is estimated that more than 100 million people worldwide have used terfenadine throughout the years

since the drug became available on the market.¹⁶ Although the drug is not currently being manufactured in the United States, it is still widely used in Canada. Moreover, fexofenadine, a metabolite of terfenadine, is presently available and widely used in the United States. Because terfenadine is rapidly and nearly completely biotransformed during a first pass to its active acid metabolite fexofenadine and because administration of terfenadine and fexofenadine result in comparable serum concentrations of the active metabolite,¹⁷ our findings address both the safety of terfenadine and fexofenadine during gestation. Because of the common occurrence of allergic conditions in women of childbearing age and because almost half of the pregnancies are unplanned,⁶ it was imperative to evaluate fetal safety. The natural course of allergic rhinitis during pregnancy may worsen in some cases, presumably by pregnancy-related hormonal changes. These hormonal changes are believed to contribute to increased nasal mucosa congestion, swelling, and discharge.¹ Terfenadine can potentially be useful during pregnancy for a variety of allergic conditions. These situations, although not life-threatening to the mother may cause a great deal of maternal discomfort and indirectly adversely affect the fetus through an effect on maternal sleeping, nutrition, and emotional status. Moreover, 2 well-established complications of nasal congestion and rhinitis are aggravation of preexisting asthma and predisposition to sinusitis.¹

The fetal safety of first-generation antihistamines was shown in a number of reports. Alkylamines (eg, chlorpheniramine) and piperazines (eg, hydroxyzine) were not associated with increased incidence of major malformations.¹⁸ Ethanolamines (eg, diphenhydramine) were not associated with increased risk for major malformations, although some concerns regarding their fetal safety have been raised after a case-control report associating maternal diphenhydramine use with oral clefts.¹⁹ Pregnancy exposure to the second-generation antihistamines astemizole and cetirizine was not associated with increased rates of major malformations.^{20,21} However, the relatively small sample size of these studies limits the strength of their conclusions.

This study, the first prospective controlled human report on the safety of terfenadine during pregnancy, did not find an association between terfenadine use during organogenesis and a 6-fold increased risk of major malformations. Although the lower birth weight observed in the terfenadine group was statistically significant, we do not assume it has a major clinical significance because the rates of birth weight below 2500 g and the rates of less than 10th percentile for gestational age did not differ between the groups. Moreover, multiple regression analysis indicated that terfenadine treatment-related factors, such as the daily dose, duration of therapy, time of exposure, the presence of maternal asthma, and concomitant steroid treatment, do not account for the lower birth weight in this group. This apparent difference may reflect a change because multiple comparisons were conducted. Alternatively, it is possible that terfenadine truly

decreases birth weight by a yet undefined mechanism.

An important limitation to our study is its power to detect a minor increase in the rate of major malformations. Our sample size is capable of detecting a 6.5-fold increase in the rate of major malformations (assuming a baseline risk of 3%) with 80% power and a *P* value of .05. It is noteworthy that the rate of major malformations refers to all kinds of malformations. However, most medications that cause an increase in adverse pregnancy outcome do so by causing an increase in specific malformations without much effect on the rate of total malformations. Therefore our study has even less power to detect an increase in the rate of specific malformation. Nevertheless, being the first study to examine the safety of terfenadine during pregnancy, our findings provide reassuring data. Future studies with larger cohorts are needed to confirm our findings and establish the safety of this agent.

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