Maternal Residential Atrazine Exposure and Risk for Choanal Atresia and Stenosis in Offspring

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Objective To assess the relationship between estimated residential maternal exposure to atrazine during pregnancy and the risk for choanal atresia or stenosis in offspring.

Study design Data for 280 nonsyndromic cases and randomly selected, population-based controls delivered between 1999 and 2008 were obtained from the Texas Birth Defects Registry. County-level estimates of atrazine levels obtained from the US Geological Survey were assigned to cases and controls based on maternal county of residence at delivery. Unconditional logistic regression was used to assess the relationship between maternal residential atrazine exposure and the risk for choanal atresia or stenosis in offspring.

Results Compared with offspring of mothers with low levels of estimated residential atrazine exposure, those with high levels had nearly a 2-fold increase in risk for choanal atresia or stenosis (aOR, 1.79; 95% CI, 1.17-2.74). A significant linear trend was also observed with increasing levels of atrazine exposure (adjusted $P = .002$).

Conclusion A link between maternal exposure to endocrine disruptors, such as atrazine, and the risk of choanal atresia is plausible based on previous findings. Our results lend further support to this hypothesis. *(J Pediatr 2013;162:581-6)*.

Choanal atresia and stenosis are characterized by a complete blockage and narrowing, respectively, of the opening between the posterior nasal cavity and the nasopharynx on the left side, right side, or both sides.[1] Choanal atresia and stenosis are the most common craniofacial abnormalities of the nose and often require multiple corrective surgeries to avoid life-threatening airway obstruction.[2,3] Despite the clinical significance of choanal atresia or stenosis, their etiology in the absence of a chromosome abnormality or a malformation syndrome or sequence is not well understood in humans.[4]

Although research into the etiology of nonsyndromic choanal atresia and stenosis is limited, several risk factors involved in endocrine function are suspected. For example, multiple studies have demonstrated that in utero exposure to hyperthyroid medications (ie, methimazole and carbimazole, a carboxy derivative of methimazole) may increase the risk for choanal atresia.[5-11] The exact mechanism of this suspected teratogenic effect is unclear, and a teratogenic role of the underlying hyperthyroidism has not been ruled out. Other mechanisms suspected to increase the risk of choanal atresia include suppression of retinoic acid and activation of fibroblast growth factor signaling pathways, both of which regulate endocrine function.[12,13]

Atrazine, the most widely used herbicide in the US, has been suggested to have teratogenic effects for other birth defects and is considered a potent endocrine disruptor (ie, a chemical that interferes with the normal function of the endocrine system).[14-18] However, to our knowledge, atrazine exposure has not been evaluated specifically in terms of choanal atresia or stenosis. Given the plausibility of a possible teratogenic effect of atrazine through endocrine disruption, we evaluated the relationship between residential maternal exposure to atrazine during pregnancy and the risk for choanal atresia or stenosis in offspring in Texas between 1999 and 2008.

Methods

Analyses were conducted using data from the Texas Birth Defects Registry, an ongoing population-based registry maintained by the Texas Department of State Health Services Birth Defects Epidemiology and Surveillance Branch. The registry uses statewide active case surveillance at hospitals, birthing centers, and midwife facilities to identify cases with birth defects, including live births, still births, and induced pregnancy terminations. Potential cases are included in the registry when a structural birth defect or chromosome abnormality is present and the mother resided in Texas at the time of delivery. Medical records data for each

BPA	British Pediatric Association
USGS	US Geological Survey

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case are abstracted, and case diagnoses are reviewed and classified using a 6-digit code defined by the Centers for Disease Control and Prevention, which is based on the British Pediatric Association (BPA) *Classification of Diseases and the International Classification of Diseases, 9th Revision*, Clinical Modification (termed BPA code hereinafter).[19] Registry data are also linked to reproductive and sociodemographic data (eg, maternal address at delivery) from birth and fetal death certificates obtained from the Vital Statistics Unit of the Texas Department of State Health Services. For the present analyses, corresponding vital records data were also obtained for potential controls, sampled from all live births in Texas during the study period. These data included infant sex, delivery date, and maternal race/ethnicity, birthplace, age, education, smoking (yes vs no), and history of live births. The protocol for this study was approved by the Institutional Review Board of the University of Texas Health Science Center at Houston.

Data for cases with documented postnatal diagnoses of choanal atresia or stenosis (BPA code 748.000) delivered between January 1, 1999, and December 31, 2008, were included in our analyses. Cases with a choanal atresia or stenosis BPA code but written comments indicating that the case did not have choanal atresia or stenosis (n = 64) were not included. To reduce the potential for etiologic heterogeneity among cases, all analyses were restricted to nonsyndromic cases (ie, those without possible diagnoses of chromosome abnormalities or malformation syndromes or sequences). Analyses were repeated in the subset of isolated cases (ie, nonsyndromic cases without additional major malformations) because of the possibility that some of the nonsyndromic cases with additional major malformations might have had undiagnosed syndromes or syndromes that have yet to be defined by the medical genetics community. We also selected a random sample of controls without major malformations delivered during the study period, using a ratio of 10 controls to 1 case.

Annual estimates of atrazine levels in all Texas counties for the period 1999-2007 were obtained from the US Geological Survey (USGS).[20] Atrazine estimates from the USGS model are based on agricultural crops (crop acreage and reported crops) that were likely to have applications of atrazine. The USGS method for developing these estimates has been described elsewhere.[20] In brief, the USGS method uses Agro-Trak survey data on pesticide use and Census of Agriculture and National Agriculture Statistics Service data on harvested crop acreages for all counties in the contiguous US. To ensure that atrazine use was accounted for in all geographic areas, atrazine crop application rates for Crop Reporting Districts not surveyed were derived from adjacent Crop Reporting Districts that had been surveyed. Crop Reporting Districts consist of multiple adjacent counties grouped to represent similar geography, climate, and cropping practices. For this assessment, data on the Texas counties were linked to maternal county of residence at the time of delivery and the year of delivery for cases and controls. Because data for 2008 were not available, 2007 atrazine data were used for 2008 deliveries. For, main analyses, atrazine exposure (pounds per square mile) was categorized as low, medium, medium-high, or high, based on the distribution of atrazine levels in controls (ie, on cutoffs below the 25th percentile, above the 25th percentile and less than the 75th percentile, above the 75th percentile and below the 90th percentile, and above the 90th percentile, as used by Reynolds et al[21]).

Statistical Analyses

The distributions of infant and maternal sociodemographic and reproductive characteristics among cases and controls were tabulated using counts and proportions and compared using the χ^2 test. The distribution of overall atrazine levels in Texas was also described by year. Furthermore, mean atrazine levels for 1999-2007 were plotted for each county.

Frequencies of cases and controls were determined for each atrazine category (ie, those based on the 25th, 75th, and 90th percentile cutoffs in controls). In the main analyses, unconditional logistic regression was used to assess the relationship between categories of atrazine exposure and choanal atresia or stenosis. Using the category of low atrazine exposure as a referent, we estimated crude ORs for each atrazine exposure level category. We also estimated ORs adjusted for the following potential confounders (based on the literature): season of conception, infant sex, birth year, and maternal race/ethnicity, education, age, and smoking. Furthermore, we estimated adjusted *P* values to assess the potential for a linear trend across increasing categories of atrazine exposure. We also assessed a linear trend using a continuous measurement of atrazine levels, based on 100-pound increments. To further limit potential heterogeneity, we repeated our main analyses in isolated cases. We also repeated our main analyses adjusting for month of conception instead of season of conception. In the main analyses, estimated atrazine exposure was based on estimates during the year of delivery, because address at conception was not available. However, we also repeated analyses using estimated atrazine exposure based on year of conception. Finally, to account for within-group correlation resulting from the use of a county-level exposure assessment, we also used mixed-effects logistic regression, adjusted for all 7 potential confounders, to assess the association between atrazine exposure and choanal atresia or stenosis. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina) and Stata version 12 (StataCorp, College Station, Texas).

Results

Between 1999 and 2008, there were 372 cases in Texas with a postnatal diagnosis of choanal atresia or stenosis. Controls were selected at random among all live births in Texas during the study period at a 10 to 1 control-to-case ratio (n = 3720 controls). Twenty-eight cases had a chromosomal abnormality, and 64 had a malformation syndrome or sequence. The main analyses focused on the remaining 280 nonsyndromic cases. The proportion of subjects missing maternal county of residence at delivery, and thus missing atrazine exposure

Table I. Characteristics of controls and nonsyndromic cases with choanal atresia in Texas, 1999-2008

Characteristic	Cases (n = 280)	Controls (n = 3720)	*P* value
Infant sex, n (%)			
Female	138 (49.5)	1813 (48.7)	.68
Male	141 (50.5)	1907 (51.3)	
Delivery year, n (%)			
1999	28 (10.0)	363 (9.8)	.65
2000	29 (10.4)	364 (9.8)	
2001	32 (11.4)	353 (9.5)	
2002	25 (8.9)	387 (10.4)	
2003	25 (8.9)	354 (9.5)	
2004	23 (8.2)	406 (10.9)	
2005	29 (10.4)	365 (9.8)	
2006	36 (12.9)	364 (9.8)	
2007	22 (7.9)	368 (9.9)	
2008	31 (11.1)	396 (10.7)	
Maternal race/ethnicity, n (%)			
Non-Hispanic white	110 (39.4)	1310 (35.2)	.41
Non-Hispanic black	30 (10.8)	447 (12.0)	
Hispanic	133 (47.7)	1831 (49.3)	
Other	6 (2.2)	130 (3.5)	
Maternal birthplace, n (%)			
US	207 (73.9)	2638 (70.9)	.21
Outside US	73 (26.1)	1082 (29.1)	
Maternal age, years, n (%)			
<20	33 (11.8)	562 (15.1)	.48
20-24	77 (27.5)	989 (26.6)	
25-29	79 (28.2)	1034 (27.8)	
30-34	56 (20.0)	755 (20.3)	
35-39	28 (10.0)	320 (8.6)	
≥40	7 (2.5)	60 (1.6)	
Maternal education, n (%)			
Less than high school	92 (33.5)	1167 (31.8)	.90
High school	79 (28.7)	1069 (29.1)	
More than high school	104 (37.8)	1439 (37.2)	
Previous live births, n (%)			
No	102 (37.5)	1388 (38.4)	.98
Yes	170 (62.5)	2231 (61.7)	
Maternal smoking, n (%)			
No	259 (92.8)	3499 (94.4)	.25
Yes	20 (7.2)	209 (5.6)	
Season of conception, n (%)			
Spring	73 (26.2)	920 (24.8)	.26
Summer	74 (26.5)	858 (23.1)	
Fall	72 (25.8)	939 (25.3)	
Winter	60 (21.5)	992 (26.8)	

level, was similar between the nonsyndromic cases and controls (0.4% [1 of 280] and 0.5% [18 of 3720], respectively).

There were no significant differences in the distribution of characteristics (ie, infant sex, delivery year, or maternal race/ethnicity, birthplace, age at delivery, education, history of previous live births, smoking, season of conception) between cases and controls (Table I). Further characteristics of a subset of these cases have been previously described in a descriptive epidemiology study.[4] The overall distribution of atrazine levels in Texas between 1999 and 2007 are presented in Table II. A map plotting atrazine exposure categories for each Texas county, based on mean atrazine application over 1997-2007, is presented in the Figure.

Offspring of mothers with high levels of estimated residential atrazine exposure had a significantly increased risk of choanal atresia or stenosis compared with those with low exposure levels (OR, 1.65; 95% CI, 1.10-2.48) (Table III).

Table II. Distribution of atrazine levels (pounds per square mile) in Texas by year, 1999-2007

Year	Mean	Median	Minimum	Maximum
1999	14.71	3.83	0.00009	194.6
2000	19.53	4.83	0.00009	223.8
2001	15.18	3.04	0.0002	211.3
2002	14.80	2.16	0.0002	235.5
2003	15.73	3.58	0.001	161.1
2004	13.82	2.28	0.0004	177.6
2005	11.89	2.47	0.0001	211.4
2006	9.24	2.27	0.0004	115.9
2007	15.68	3.03	0.0006	352.5

A similar association was observed after adjustment for season of conception, infant sex, birth year, and maternal race/ethnicity, education, age, and smoking (aOR, 1.79; 95% CI, 1.17-2.74). The unadjusted and adjusted magnitudes of association across the categories of exposure were consistent with a dose-response over increasing levels of atrazine exposure. A significant linear trend was also observed with increasing category of atrazine exposure (adjusted $P = .002$). Main analyses were also repeated using a continuous measure of atrazine exposure (ie, based on 100 pound per square mile increments). A significant linear increase was observed (OR, 1.40; 95% CI, 1.04-1.89; aOR, 1.49; 95% CI, 1.09-2.04). All of these main results were similar to results from analyses repeated using estimated atrazine exposure based on year of conception instead of delivery and analyses repeated adjusting for month of conception instead of season.

To further limit heterogeneity, analyses were repeated among isolated cases (n = 147). The results from these analyses were similar to the main results (data not shown). Additionally, results from the mixed-effects logistic regression model were similar to the results obtained using unconditional logistic regression (data not shown).

Discussion

We found a significant association between the estimated maternal residential exposure to atrazine and the risk for nonsyndromic or isolated choanal atresia or stenosis in offspring. Specifically, the prevalence of choanal atresia or stenosis was highest in offspring of women who lived in counties with the highest estimated levels of atrazine use. Our results suggest a monotonic dose–response relationship, whereby living in counties with increasing atrazine application is associated with increasing risk of having a child with choanal atresia or stenosis.

Given the lack of large-scale population-based measurements of personal atrazine exposure, our exposure assessment strategy was based on county-level estimates of atrazine application provided by the USGS, and thus our results should be interpreted with caution. Nonetheless, living in areas with high levels of atrazine application (eg, proximity to agricultural fields) appears to correlate with personal exposure.[15,22] For instance, families living in farm households

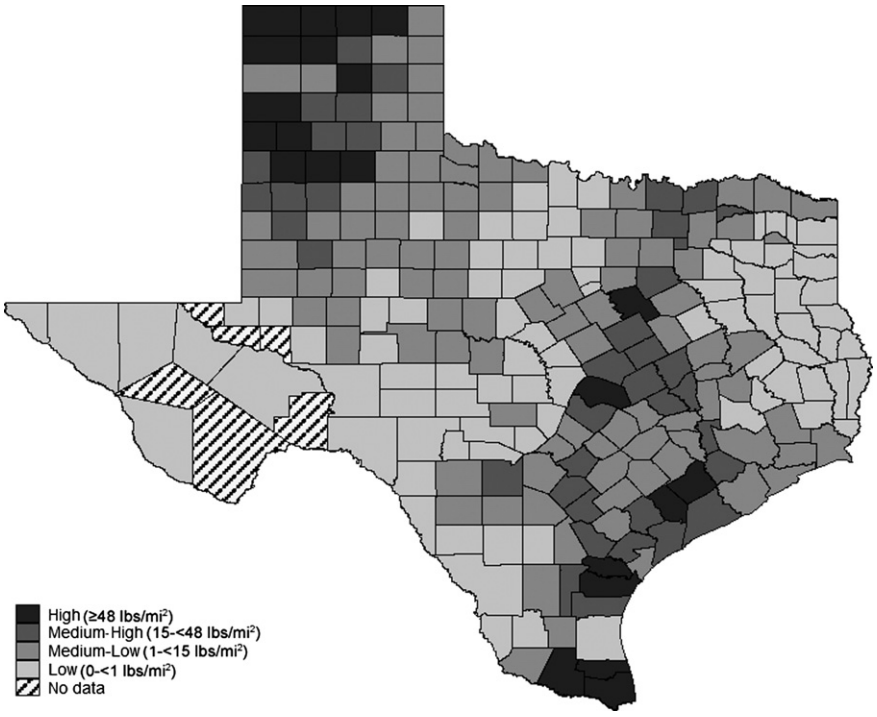

Figure. Distribution of mean atrazine levels in Texas by county, 1999-2007.

have higher levels of urine atrazine metabolites compared with those in nonfarm households.[22]

Based on research using animal models, the primary target of atrazine toxicity is the female reproductive system, and there is growing interest in the association between atrazine exposure in humans and birth defects.[15] Although the relationship between maternal atrazine exposure and the risk for choanal atresia or stenosis has not been evaluated previously, our findings are consistent with previous reports of associations between atrazine exposure and adverse outcomes of pregnancy and other birth defects, including gastroschisis, spina bifida, cleft lip, congenital heart defects, limb reduction defects, and urogenital defects.[15-18]

In addition, because atrazine is a suspected endocrine disruptor in humans (including disruption of thyroid hormone), and evidence has been published linking the risk of choanal atresia with in utero exposure to hyperthyroid medications, it is plausible that choanal atresia may be an atrazine-susceptible phenotype.[5-11] Even though the pathways involved in atrazine-induced tertatogenesis have not yet been elucidated (particularly for choanal atresia), 3 potential mechanisms warrant further exploration. First, it is possible that atrazine may interfere with maternal thyroid hormone levels during pregnancy, thereby increasing the risk of choanal atresia. Second, atrazine exposure (and exposure to other endocrine disruptors) may lead to maternal hyperthyroidism before pregnancy. Third, previous studies in mice have shown that the risk for choanal atresia or stenosis increases with suppression of retinoic acid synthesis (ie, vitamin A deficiency) or activation of fibroblast growth factor signaling pathways.[12,13] Although the relationships among the thyroid hormone, retinoic acid, and fibroblast growth factor signaling pathways during development are not fully understood, it has been suggested that retinoic acid regulates thyroid function, and that thyroid hormones regulate fibroblast growth factor receptor signaling.[23,24] Although whether atrazine might be involved in retinoic acid synthesis or fibroblast growth factor signaling is unclear, precursors or derivatives of atrazine possibly may be involved.

Table III. Association between atrazine and choanal atresia in Texas, 1999-2008

Atrazine level*	Pounds per square mile	Cases (n = 280), n (%)†	Controls (n = 3720), n (%)	OR	95% CI	aOR‡	95% CI
Low (reference)	0 to <1.40	64 (22.9)	922 (24.9)	1.00		1.00	
Medium-low	1.40 to <15.03	120 (43.0)	1856 (50.1)	0.93	0.68-1.27	0.93	0.68-1.29
Medium	15.03 to <47.63	53 (19.0)	557 (15.1)	1.37	0.94-2.00	1.35	0.90-2.01
High	≥47.63	42 (15.1)	367 (9.9)	1.65	1.10-2.48	1.79	1.17-2.74

*Atrazine categories based on 25th, 75th, and 90th percentiles in controls.
†Nonsyndromic cases.
‡ORs adjusted for season of conception, infant sex, birth year, and maternal race/ethnicity, education, age, and smoking.

This study must be considered in light of certain limitations. Given that the critical period for exposure for choanal atresia is early in pregnancy,[25] residential atrazine exposure based on maternal residence at the time of delivery might not have accurately represented residential atrazine exposure during the critical period in all subjects. However, we have previously shown that residential mobility from one county to another between conception and delivery is infrequent in Texas (≤6%) and is expected to occur at similar proportions between cases and controls.[26] A small proportion of subjects (3%) were expected to have resided in a different state at conception, but residential mobility during pregnancy is not expected to result in a meaningful change in county-based exposure assessment in this population.[26] As stated earlier, we used a county-based estimate of atrazine exposure in the present study, which might not adequately account for variability of exposure within counties or within years; however, no large-scale population-based measures of personal exposure are available to evaluate this relatively rare phenotype. Thus, the present study is an important first step in identifying possible associations. Although we adjusted for several potential confounders, we cannot rule out the possibility of confounding by unmeasured variables. Future research using other exposure assessment methodologies, including biomarkers of exposure, is needed to confirm our findings. We were also limited in our case sample size, owing to the rarity of choanal atresia and stenosis.

Despite the foregoing limitations, the present study had several strengths, including the use of a sample that used active surveillance to identify cases. The sample also included cases that were stillbirths and elective pregnancy terminations, which reduced the potential for selection bias. Although choanal atresia or stenosis is a rare condition, the Texas Birth Defects Registry represents one of largest population-based birth defects registries in the world, and our sample contained more cases with nonsyndromic choanal atresia or stenosis than most previous studies evaluating potential risk factors for choanal atresia or stenosis. In addition, to reduce heterogeneity, we restricted our case definition to nonsyndromic cases and also considered isolated cases separately.

In summary, we report an association between maternal atrazine exposure and the risk for choanal atresia or stenosis. Our findings, in conjunction with previous studies, suggest an important role of maternal endocrine disruption in risk for choanal atresia or stenosis. If confirmed, future research evaluating the many other factors that influence endocrine function may shed further light on the etiology of choanal atresia or stenosis. ■

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