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Vasoactive Exposures during Pregnancy and Risk of Microtia

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Abstract

Background—Little is known about the etiology of nonsyndromic microtia. This study investigated the hypothesis that microtia is caused by vascular disruption.

Methods—The study analyzed data from the population-based National Birth Defects Prevention Study (NBDPS) for deliveries between 1997 and 2005. Four hundred eleven nonsyndromic cases of microtia, with or without additional defects, were compared to 6560 nonmalformed infants with respect to maternal exposures to vasoactive medications and smoking during the periconceptional period and conditions that have previously been associated with vascular events (multiple gestation, maternal history of type 1, type 2, or gestational diabetes, and hypertension). Odds ratios (ORs) were estimated with multivariable models, controlling for the effects of race/ethnicity, education, periconceptional folic acid use, and study center.

Results—Risk estimates for vasoactive medications and smoking were not meaningfully increased. Maternal type 1/2 diabetes was diagnosed before or during the index pregnancy in 4% and 1% of cases, respectively, compared to 1% and 0.05% of controls; the adjusted OR for these two groups combined was 7.2 (95% confidence interval [CI], 3.9–13.1). Gestational diabetes was observed for 9% of cases and 6% of controls; the OR was moderately elevated (OR, 1.4; 95% CI, 0.9–2.0). ORs were also increased for multiple gestations (OR, 2.5; 95% CI, 1.5–4.2) and pre-existing hypertension (OR, 1.6; 95% CI, 1.0–2.5).

Conclusions—Because ORs were only elevated for diabetes and not for vasoactive exposures or other potential vascular events, findings suggest that some microtia occurrences may be part of the diabetic embryopathy rather than manifestations of vascular disruption.

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Dr. Werler serves on the advisory board of studies that evaluate the effects of medications taken in pregnancy for rheumatoid arthritis. It is possible that the manufacturers of these medications also make drugs that were examined in this article. Dr. Werler does not track manufacturer's product lines. Therefore, we believe there is no conflict of interest. Dr. Mitchell owns Johnson & Johnson stock valued at less than $20,000, and the company makes a number of the products under study; the company had no involvement in or knowledge of this analysis. Dr. Moore and Ms. Van Bennekom report no conflicts of interest.

Keywords

birth defect; microtia; anotia; ear; epidemiology; diabetes mellitus; pregnancy; medication

Introduction

Microtia is a birth defect of the external ear that can vary in presentation from minor changes in the external ear's size or structure to its most severe form, anotia, in which the external ear and auditory canal are absent. It may present as an isolated defect or with other defects and is also a component of several syndromes including Goldenhar, Treacher Collins, and Nager (Harris et al., 1996; Alasti and Van Camp, 2009).

Descriptive epidemiologic studies have reported associations between microtia and older maternal age (Harris et al., 1996; Forrester and Merz, 2005; Canfield et al., 2009), lower maternal educational attainment (Shaw et al., 2004; Husain et al., 2008; Canfield et al., 2009), multiple births (Shaw et al., 2004; Forrester and Merz, 2005), and male infant sex (Harris et al., 1996; Shaw et al., 2004; Forrester and Merz, 2005; Canfield et al., 2009). Previous studies have found that compared to non-Hispanic whites, Hispanics (Harris et al., 1996; Shaw et al., 2004; Husain et al., 2008; Canfield et al., 2009) and Asians (Harris et al., 1996; Forrester and Merz, 2005) have increased risk, and non-Hispanic blacks (Husain et al., 2008; Canfield et al., 2009) have lower risk. Several studies, including one that examined earlier data from the same source used in our study, have reported an association between microtia and maternal diabetes (Mastroiacovo et al., 1995; Wang et al., 2002; Correa et al., 2008).

Single gene defects and chromosomal abnormalities have been identified for several syndromes that include microtia, such as Townes–Brocks, branchio-oto-renal, and DiGeorge (Alasti and Van Camp, 2009; Luquetti et al., 2011), but much remains unknown about the etiology of nonsyndromic occurrences of this malformation. Several hypotheses have been proposed, however. One causal mechanism hypothesizes that the neural crest cell formation, migration, and proliferation necessary for normal development of the ear are altered by one or more factors (Johnston et al., 1990; Luquetti et al., 2011). Wang et al. (2002) proposed that maternal diabetes may be one such factor. Castilla et al. (1999) proposed that chronic hypoxia observed among mothers living at high altitude may be another. Lammer et al. (1985) proposed that retinoic acid may cause deficiencies in the cephalic neural crest cells resulting in the retinoic acid embryopathy, which includes microtia and other craniofacial defects, as well as defects of the heart, thymus, and central nervous system.

Another potential causal mechanism is vascular disruption, a mechanism that also has been proposed for several other birth defects (Van Allen, 1981). Animal (Newman and Hendrickx, 1981; Escobar and Liechty, 1998) and clinical (Hoyme et al., 1981; Vargas et al., 2000; Werler et al., 2004a; Werler et al., 2009) studies offer support for this causal mechanism for a variety of birth defects. Vasoactive exposures considered in studies that tested the vascular disruption hypothesis include medications and illicit drugs with vasodilatory or vasoconstrictive properties (Martin et al., 1992; Werler et al., 2004a; Werler et al., 2009) and cigarette smoking, which is mildly vasoconstrictive (Werler et al., 2003;

Werler et al., 2004a). Conditions that might be markers of vascular events such as diabetes, hypertension, and multiple gestations have also been studied in association with various purported vascular disruption defects (Lawson et al., 2002; Werler et al., 2004a; Verona et al., 2006; Husain et al., 2008). However, other than a study by Lawson et al. (2002) that observed an association between multiple gestations and microtia, studies have not explored microtia as a vascular disruption defect. In this study, we examined the associations between maternal vasoactive exposures and possible vascular events and the risk for microtia.

Methods

We analyzed data collected by the National Birth Defects Prevention Study (NBDPS), an ongoing, multisite, population-based, case-control study of environmental and genetic risk factors associated with selected major structural birth defects (Yoon et al., 2001). Birth defects surveillance systems in 10 states in the United States (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey [ending in 2002], New York, North Carolina [beginning in 2003], Texas, and Utah [beginning in 2003]) ascertain case infants using standardized, detailed case definitions of over 30 defects and report them to the NBDPS. Each site also identifies a random sample of nonmalformed control infants from birth certificates or birth hospital data for the same geographic regions and time periods as case infants. Mothers of case and control infants who agree to participate are contacted within 24 months after their estimated date of delivery (EDD). Using a computer-assisted telephone interview in English or Spanish, trained interviewers collect information on family demographics, maternal medical history, pregnancy history, and behaviors. When mothers report a specific illness or condition (e.g., hypertension, fever), they are asked about medications taken for this illness. They are also read a list of specific medications and asked about the use of each; they are also asked about their use of illicit drugs, including specific questions on cocaine, crack, and amphetamines. Drugs are coded using the Boston University Slone Epidemiology Center Drug Dictionary (Kelley et al., 2003). For this analysis, we included information from mothers with delivery dates between October 1, 1997, and December 31, 2005. The institutional review boards for each site approved the NBDPS protocol.

Outcome

Information abstracted from medical records for case infants is reviewed by a clinical geneticist who first ensures that each case meets the predefined diagnostic criteria and then classifies the occurrence of birth defects in each case as either “isolated” (i.e., microtia occurring in isolation, with other minor anomalies, or with major structural anomalies presumed to be secondary to a shared primary defect) or “multiple” (i.e., microtia occurring with other presumably unrelated major structural defects). Details of this review have been described previously (Rasmussen et al., 2003). For this analysis, cases classified as isolated and multiple comprised the case group. Infants whose microtia was part of the oculoauriculovertebral spectrum (OAVS), which includes ear as well as eye, craniofacial, or vertebral defects, were classified as isolated or multiple based on the non-ear structural defects using the schema above. Infants with known chromosomal abnormalities or single-gene disorders are excluded from NBDPS.

Exposure

We considered two categories of maternal vasoactive exposures, medications and cigarette smoking, and three categories of potential vascular events, diabetes, hypertension, and multiple gestation. The time period of interest for medication and smoking exposures was 1 month before conception through the third month of pregnancy. We identified any use of medications with vasoactive properties including decongestants, antimigraine triptans and ergots, amphetamines, cocaine, bronchodilators, antihypertensives, and nonsteroidal anti-inflammatory drugs; exposures to both single component and multicomponent medications were included. Cigarette smoking was classified according to the number of cigarettes smoked per day in the exposure period (no smoking, 1–14 cigarettes per day, ≥15 cigarettes per day). Diabetes was classified according to its type and the timing of diagnosis, resulting in four groups: no diabetes, type 1 or type 2 diabetes diagnosed before the index pregnancy, type 1 or type 2 diabetes diagnosed during the index pregnancy, and gestational diabetes; subsequently type 1 and type 2 diabetes are combined and referred to as “diabetes.” Although mothers who report diabetes are asked about the type of diabetes they have and are read a list of specific types, we were concerned that some mothers who reported diabetes diagnosed during pregnancy may, in fact, have had gestational diabetes. We therefore reviewed the interview records for these women and determined that all but one reported being diagnosed within the first 2 months of pregnancy, suggesting that this was not gestational diabetes, but likely pre-existing diabetes that was undiagnosed until pregnancy onset. The number of women with diabetes diagnosed during pregnancy was small, prompting us to combine these women with those diagnosed before the index pregnancy. Hypertension was classified according to the timing of the diagnosis, resulting in three groups: no hypertension, hypertension diagnosed before the index pregnancy, and hypertension diagnosed during the index pregnancy. For plurality, pregnancies were classified as single or multiple gestations.

Statistical Analysis

We calculated crude and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the associations between the purported vasoactive exposures and the occurrence of microtia using a multivariable logistic regression model with terms for each of the exposures. For adjusted analyses, we examined the following potential confounders: maternal age at delivery (<20 years, 20–29 years, ≥30 years), binge alcohol use during the month before or the first 3 months of pregnancy (>4 drinks in one sitting; alcohol use, but not binge use; no use), pre-pregnancy body mass index (BMI; underweight, <18.5 kg/m^2; normal weight, 18.5–<25 kg/m^2; overweight, 25–<30 kg/m^2; obese, ≥30 kg/m^2), education (<12 years, 12 years, ≥13 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), folic acid use 1 month before conception through month 1 of pregnancy (any, none), infant sex (male, female, other/missing), number of previous live births (0, ≥1), study site, intent to become pregnant (yes/did not care, no), and year of infant's birth. Those that changed any of the estimated associations for the main effects by 10% or more were included in the adjusted analyses; these were education, race/ethnicity, periconceptional folic acid use, and study center. Separate analyses were conducted for any microtia (defined as occurrence of microtia as an isolated or multiple defect) and for isolated microtia. Because interviews were conducted up to 2 years after the EDD, we were concerned that as the time to interview

increased, errors in the reporting of exposures would increase. We were especially concerned that errors would be more common among control mothers than case mothers, which would result in biased odds ratios (ORs) among those with longer intervals to the interview. To address this issue of recall error, we also estimated the main effects stratified by the time from EDD to the interview date (<1 year from EDD vs. ≥1 year). All analyses were conducted with the statistical software package SPSS version 16.0.

Results

The case group was comprised of 423 infants diagnosed with microtia; 306 (72%) had isolated microtia and 117 (28%) had multiple defects. The control group was comprised of 6807 nonmalformed infants. We excluded two case infants (both had isolated defects) and 60 control infants because their mothers did not complete the medication section of the interview. Our final sample included 421 case infants (304 with isolated defects) and 6747 control infants. The distributions of maternal characteristics for both cases and controls are provided in Table 1. Compared to mothers of control infants, mothers of infants in both the any microtia and isolated microtia case groups were less likely to be of non-Hispanic white race/ethnicity, to have 12 or more years of education, to have higher household incomes, to be born in the United States, and to have used periconceptional folic acid.

Among the mothers of case infants, there were no exposures to triptans or ergots from the month before pregnancy through the third month of pregnancy. Because only two case mothers (0.5%) and 40 control mothers (0.6%) reported taking amphetamines during the time period of interest, we did not include this exposure as a term in our models (data not shown). Table 2 presents the distributions for the other vasoactive exposures and markers of vascular events for cases and controls and aORs and 95% CIs. For this analysis, we included those with complete covariate data: 411 cases with any microtia (97.2% of eligible cases) and 6560 controls (96.4% of eligible controls); 296 of the cases were classified as isolated and 115 as multiple. Compared with control mothers, mothers of case infants were more likely to have diabetes (among case mothers with diabetes, 60% reported having type 1 diabetes and 40% reported having type 2 diabetes; among control mothers, these proportions were 45% and 55%, respectively). Nevertheless, it is important to note that the number of mothers with these conditions was small (4.9% of cases and 0.6% of controls); 3.9% of case mothers were diagnosed before the index pregnancy compared to 0.6% of control mothers, and 1.0% of case mothers were diagnosed during the index pregnancy compared to 0.05% of control mothers. For the occurrence of any microtia, we observed an aOR of 7.2 (95% CI, 3.9–13.1) for diabetes diagnosed before or during the index pregnancy. For gestational diabetes, the aOR was 1.4 (95% CI, 0.9–2.0). Although most of the infants of mothers with diabetes had multiple defects, the aOR also was elevated when we included only infants with isolated microtia: aORs were 3.4 (95% CI, 1.3–8.5) for diabetes diagnosed before or during the index pregnancy and 1.4 (95% CI, 0.9–2.2) for gestational diabetes. Compared with control mothers, mothers in both case groups also were somewhat more likely to report cocaine use and to have had a multiple gestation, and mothers in the any microtia case group were slightly more likely to report hypertension diagnosed before pregnancy. For the other putative vasoactive exposures, we observed no evidence of associations with an increased risk for microtia.

We identified the specific birth defects observed in the 115 infants with microtia classified as multiple, and there was no clear pattern of birth defects according to diabetes status. Of the 14 diabetes-exposed cases, the multiple structural defects were as follows: OAVS and cardiac defects (3); OAVS, cardiac defects, and hydrocephaly (1); OAVS and cleft lip and palate (1); OAVS, sacral agenesis and cardiac defects (1); microtia, sacral agenesis, cardiac and central nervous system defects (1); microtia, cleft palate, cardiac defects, and limb deficiency (1); microtia, cardiac defects and either sacral agenesis, clubfeet, or hydrocephaly (3); and microtia and cardiac defects (3).

In our analysis, stratified by time to interview, the results were similar for mothers interviewed less than 1 year from their EDD and those interviewed 1 year or more from EDD.

Discussion

We investigated the association between risk of microtia and maternal vasoactive exposures and markers of vascular events to test the hypothesis that vascular disruption influences the development of this defect. Our findings do not support this hypothesis as only maternal diabetes diagnosed before or during the index pregnancy showed a strong and stable association with microtia suggesting instead that diabetic embryopathy may be involved. The diabetes association was observed for both overall and isolated microtia, although it was weaker for isolated microtia; these results are similar to those reported by Correa et al. (2008) using earlier data from the same source with approximately one-third fewer cases and controls and approximately half as many reports of maternal diabetes. Our OR of 7.2 for any microtia is similar to the OR of 6.3 reported by Werler et al. (2004b) in another case-control study. The relationship between maternal glycemic control and microtia in our study seemed to be hierarchical. We might expect that women with diabetes diagnosed during pregnancy would have the poorest glycemic control in early pregnancy under the assumption that they had pre-existing diabetes that remained undiagnosed until a first prenatal visit. Diabetes diagnosed during pregnancy was approximately 20 times more common in case (0.97%) than control mothers (0.05%). Because women with pre-existing diabetes have had the opportunity for treatment before pregnancy, their glycemic control in early pregnancy might be better than those diagnosed during pregnancy, but worse than gestational or nondiabetic women. This is consistent with our observation that the proportion of case mothers with pre-existing diabetes (3.89%) was approximately seven times that of control mothers (0.59%), whereas the corresponding proportions for gestational diabetes (9.0% and 6.1%) reflected an aOR of only 1.4. If we take the hierarchical response one step further, we might also expect that, relative to nonobese women, obese women would have poorer glycemic control as a result of insulin resistance and their offspring would have a higher risk for microtia; this expectation is supported by an OR of 1.3 for obesity and microtia reported in another analysis of NBDPS data (Ma et al., 2010). As noted in the Methods section, we examined BMI as a potential confounder, but it did not meet our criterion for inclusion in the multivariable models.

In rat embryos, a critical level of glucose was necessary for malformations to occur, and above that threshold, the malformation rate increased exponentially as the glucose level

increased (Reece and Homko, 2000). Wang et al. (2002), in a clinical study, found the risk for OAVS was higher for maternal gestational diabetes (OR, 2.3; 95% CI, 1.0–4.8) than maternal pre-existing type 1 or 2 diabetes (OR, 1.5; 95% CI, 0.1–10.0) suggesting poorer glycemic control among women with gestational compared to those with pre-existing diabetes. We did not see a relationship between maternal diabetes and OAVS in this study; however, the clinical diagnosis of OAVS can be challenging and possibly subjective at the milder end of the spectrum. We likely under-ascertained OAVS when minor anomalies such as mild facial asymmetry/mandibular hypoplasia or facial nerve palsy were present. However, it seems doubtful that such under ascertainment would differ by maternal diabetes status because OAVS in association with maternal diabetes is not widely known. When Wang et al. (2002) examined microtia and other types of ear defects combined, ORs for gestational diabetes (OR, 1.2; 95% CI, 0.9–1.6) and pre-existing diabetes (OR, 0.9; 95% CI, 0.5–1.8) approximated the null. In contrast, our more homogeneous case group of microtia but not other ear defects produced an aOR of 1.4 (95% CI, 0.9–2.0) for gestational diabetes and an aOR of 7.2 (95% CI, 3.9–13.1) for diabetes diagnosed before or during pregnancy.

Husain et al. (2008), in a study using data from a birth defects registry, noted that the risk factors identified for microtia differed from those identified for other defects with a purported vascular disruption mechanism, which lends support for a causal mechanism for microtia other than vascular disruption. Sadler and Rasmussen (2010) explored whether a vascular mechanism explained the development OAVS and found the experimental and clinical evidence inconclusive; they found stronger evidence to support a mechanism involving abnormal neural crest cell development. Hyperglycemia caused oxidative stress and inhibited the Pax 3 gene, which is responsible for neural crest cell development in rodent embryos (Zabihi and Loeken, 2010). However, nicotine has also been purported to cause oxidative stress, but both the present and another study observed no association between microtia and smoking (Mastroiacovo et al., 1995).

A number of animal and clinical studies have suggested that maternal alcohol use alters neural crest cell migration resulting in defects of structures derived from these cells (Sulik et al., 1988; Werler et al., 1991; Johnston and Bronsky, 1995; Sant'Anna and Tosello, 2006). If this alteration in neural crest cell migration were involved in the development of microtia, we would expect to see an association with alcohol in our study, but we did not (Table 1). However, the pathogenetic mechanisms that lead to abnormal ear development are not well understood, and abnormal neural crest cell migration may be only one causal component. Further, measurement error may have prevented our study from identifying an association with maternal alcohol use.

Our findings add to the evidence that diabetic embryopathy might also include microtia. Other embryopathies, such as fetal warfarin (Hall et al., 1980; Stevenson et al., 1980; Iturbe–Alessio et al., 1986; Bates et al., 2004) and rubella syndrome (Gregg, 1941; Webster, 1998; De Santis et al., 2006; Morice et al., 2009), constitute well-defined phenotypes with distinct sets of affected structures. Diabetic embryopathy, on the other hand, is applied to a wide range of structural anomalies occurring among offspring of diabetic women, including cardiovascular, neural tube, musculoskeletal, gastrointestinal, and genitourinary defects and caudal regression sequence; infants often have multiple defects (Becerra et al., 1990;

Ferencz et al., 1990; Erickson, 1991; Ramos–Arroyo et al., 1992; Sheffield et al., 2002; Ray et al., 2004). Although the magnitude of the association with diabetes was higher for microtia in combination with other major structural defects, the corresponding 3.4-fold increased risk for isolated microtia suggests it alone might be another manifestation of the embryopathy.

This study had several limitations. The information on exposures was obtained via interviews of mothers conducted as long as 2 years after the EDD and consequently is subject to exposure recall error and misclassification. However, we observed little difference in our results when stratified by the time to interview, suggesting that recall by cases and controls was similar regardless of when the information was obtained. Also, with retrospective collection of exposure information, recall bias is a concern. If differential reporting of exposure information occurred between case and control mothers, we would expect control mothers to underreport medication use; the absence of associations for most exposures suggests this generally did not occur. For reporting of smoking and recreational drug use, both nondifferential and differential underreporting are possible and may have occurred in this study. For example, the number of exposures to cocaine and amphetamines reported by both case and control mothers was very small. Misclassification of the timing of medication exposures was possible, particularly for those used intermittently. However, the structured interview questions on illnesses and medication use likely improved accurate recall of exposure dates. Misclassification of the type of diabetes was also possible, especially for mothers who reported diabetes diagnosed during early pregnancy who may indeed have had gestational diabetes. However, the ORs for early pregnancy diabetes diagnosis were similar to those for pre-existing diabetes, which suggests our combining the two groups of women was appropriate. Many of the exposures we investigated, including diabetes, were reported by only small numbers of women making the results relatively unstable. In addition, although we considered potential confounders in our analyses, unidentified factors may have confounded our results. Finally, because the diagnostic information for cases was obtained via medical record review, the accuracy of these data is dependent on the thoroughness of the clinical evaluation, the completeness of documentation of the phenotype, and the appropriateness of assigned diagnostic codes used to ascertain the record. Although it is unlikely that these parameters would vary by maternal exposures for the studied defect, microtia, there could be an effect on the identification of additional major birth defects.

Our study also had strengths. Case and control ascertainment was population-based and from geographically diverse areas of the United States. The medical records of case infants were reviewed by a clinical geneticist and classified according to predefined, standardized criteria. Classification of medication exposures was also standardized by use of the Slone Drug Dictionary.

Our large, population-based, case-control study did not find associations between the occurrence of microtia and vasoactive exposures, but instead observed an association with maternal diabetes. Further investigation of the underlying causal pathways involved in diabetic embryopathy will help us better understand the risk factors for microtia.

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Table 1

Characteristics of Cases with Microtia (Any and Isolated) and Controls, National Birth Defects Prevention Study, 1997–2005

	Any microtia (n = 421) N (%)	Isolated microtia (n = 304) N (%)	Controls (n = 6747) N (%)
Maternal age at delivery (years)			
<20	50 (12)	38 (13)	719 (11)
20–29	212 (50)	147 (48)	3327 (49)
30+	159 (38)	119 (39)	2701 (40)
Maternal race			
Non-Hispanic white	155 (37)	101 (33)	4021 (60)
Non-Hispanic black	12 (3)	7 (2)	767 (11)
Hispanic	223 (53)	170 (56)	1497 (22)
Other	28 (7)	23 (8)	433 (6)
Missing	3 (1)	3 (1)	29 (<1)
Maternal education (years)			
<12	126 (30)	92 (30)	1130 (17)
12	106 (25)	77 (25)	1652 (25)
13+	187 (44)	134 (44)	3916 (58)
Missing	2 (1)	1 (<1)	49 (1)
Periconceptional folic acid use			
Yes	161 (38)	110 (36)	3429 (51)
No	260 (62)	194 (64)	3318 (49)
Study site			
Arkansas	26 (6)	20 (7)	839 (12)
California	104 (25)	79 (26)	851 (13)
Georgia	23 (6)	17 (6)	733 (11)
Iowa	23 (6)	13 (4)	759 (11)
Massachusetts	39 (9)	26 (9)	856 (13)
New Jersey	53 (13)	41 (14)	573 (9)
New York	27 (6)	19 (6)	598 (9)
North Carolina	10 (2)	8 (3)	397 (6)
Texas	88 (21)	59 (19)	772 (11)
Utah	28 (7)	22 (7)	369 (6)
Wanted to become pregnant			
Yes/did not care	295 (70)	221 (73)	4789 (71)
No	64 (15)	37 (12)	668 (10)
Missing	62 (15)	46 (15)	1290 (19)
Parity			
0	163 (39)	120 (40)	2709 (40)
1+	258 (61)	184 (61)	4031 (60)
Missing	0 (0)	0 (0)	7 (<1)
Binge alcohol use (≥4 drinks/sitting)[a]			

	Any microtia (n = 421) N (%)	Isolated microtia (n = 304) N (%)	Controls (n = 6747) N (%)
Yes	47 (11)	33 (11)	814 (12)
Alcohol use, but not binge	94 (22)	68 (22)	1629 (24)
No alcohol use	276 (66)	201 (66)	4215 (63)
Missing	4 (1)	2 (1)	89 (1)
Infant sex			
Male	242 (58)	181 (60)	3412 (51)
Female	179 (43)	123 (41)	3330 (49)
Other/missing	0 (0)	0 (0)	5 (<1)
Birth year			
1997	8 (2)	8 (3)	113 (2)
1998	40 (10)	28 (9)	750 (11)
1999	62 (15)	47 (16)	871 (13)
2000	61 (15)	44 (15)	898 (13)
2001	56 (13)	39 (13)	790 (12)
2002	40 (10)	28 (9)	685 (10)
2003	44 (11)	30 (10)	897 (13)
2004	65 (15)	45 (15)	892 (13)
2005	45 (11)	35 (12)	851 (13)
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	20 (5)	13 (4)	360 (5)
Normal (18.5–<25)	203 (48)	145 (48)	3617 (54)
Overweight (25–<30)	81 (19)	63 (21)	1454 (22)
Obese (≥30)	74 (18)	50 (16)	1046 (16)
Missing	43 (10)	33 (11)	270 (4)
Annual household income			
<$10,000	109 (26)	75 (25)	1080 (16)
$10,000–50,000	189 (45)	140 (46)	2887 (43)
>$50,000	90 (21)	63 (21)	2132 (32)
Missing	33 (8)	26 (9)	648 (10)
Maternal birthplace			
United States	249 (59)	167 (55)	5412 (80)
Outside United States	170 (41)	136 (45)	1290 (19)
Missing	2 (<1)	1 (<1)	45 (1)

[a]Use in 1 month before through month 3 of pregnancy. BMI, body mass index.

Table 2

Vasoactive Exposures for Mothers of Infants with Microtia (Any and Isolated) and Mothers of Infants with No Major Birth Defects, National Birth Defects Prevention Study, 1997–2005

	Any microtia (n = 411) Exposed		Isolated microtia (n = 296) Exposed		Controls (n = 6560) Exposed		Any microtia	Isolated microtia
Exposure	**No.**	**%**	**No.**	**%**	**No.**	**%**	**aOR (95% CI)[a]**	**aOR (95% CI)[a]**
NSAIDs	105	25.5	76	25.7	1740	26.5	1.2 (1.0–1.6)	1.3 (1.0–1.8)
Decongestants	24	5.8	13	4.4	674	10.3	0.7 (0.5–1.1)	0.5 (0.3–1.0)
Bronchodilators	11	2.7	8	2.7	199	3.0	0.9 (0.5–1.8)	1.0 (0.5–2.2)
Antihypertensives	6	1.5	3	1.0	68	1.0	1.1 (0.5–2.9)	0.9 (0.3–3.1)
Cocaine	6	1.5	4	1.4	37	0.6	1.6 (0.7–4.2)	1.7 (0.6–5.0)
Unknown vasoactive[b]	17	4.1	12	4.1	262	4.0	1.0 (0.6–1.7)	1.1 (0.6–2.0)
Cigarettes								
<14/day	50	12.2	34	11.5	871	13.3	1.0 (0.7–1.4)	1.0 (0.7–1.5)
≥15/day	17	4.1	10	3.4	374	5.7	1.1 (0.6–1.8)	0.9 (0.5–1.7)
Diabetes								
Pre-existing (type 1 or 2)	16	3.9	4	1.4	39	0.6		
Diagnosed during index pregnancy (type 1 or 2)	4	1.0	2	0.7	3	<0.1}	7.2 (3.9–13.1)	3.4 (1.3–8.5)
Gestational	37	9.0	28	9.5	397	6.1	1.4 (0.9–2.0)	1.4 (0.9–2.2)

	Any microtia (n = 411) Exposed		Isolated microtia (n = 296) Exposed		Controls (n = 6560) Exposed		Any microtia	Isolated microtia
Exposure	**No.**	**%**	**No.**	**%**	**No.**	**%**	**aOR (95% CI)[a]**	**aOR (95% CI)[a]**
Hypertension								
Pre-existing	21	5.1	10	3.4	257	3.9	1.6 (1.0–2.5)	1.1 (0.6–2.1)
Diagnosed during index pregnancy	42	10.2	31	10.5	630	9.6	1.1 (0.8–1.6)	1.2 (0.8–1.8)
Multiple gestation	18	4.4	9	3.0	168	2.6	2.5 (1.5–4.2)	1.7 (0.8–3.5)

[a] Adjusted for race/ethnicity, education, periconceptional folic acid use, and study center. For each exposure, reference category comprises women who were not exposed.

[b] Includes mothers who reported use of unknown analgesic, decongestant, or diuretic, or whose timing of vasoactive medication was unknown.

aOR, adjusted odds ratio; CI, confidence interval; NSAIDS, nonsteroidal anti-inflammatory drugs.